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Authors

Wang, Dan

Sun, Yan

Zhu, Ya-Juan

et al.

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Original Article

Comparison of opioid-free and opioid-inclusive propofol anaesthesia for thyroid and parathyroid surgery: a randomised controlled trial

Dan Wang,[1,2] **Yan Sun,**[1,2] **Ya-Juan Zhu,**[1,2] **Xi-Sheng Shan,**[1,2] **Hong Liu,**[3] **Fu-Hai Ji**[1,2] and **Ke Peng**[1,2]

1 Department of Anaesthesiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
2 Institute of Anaesthesiology, Soochow University, Suzhou, Jiangsu, China
3 Department of Anaesthesiology and Pain Medicine, University of California Davis Health, Sacramento, CA, USA

Summary

Background Postoperative nausea and vomiting occur frequently following thyroid and parathyroid surgery and are associated with worse patient outcomes. We hypothesised that opioid-free propofol anaesthesia would reduce the incidence of postoperative nausea and vomiting compared with opioid-inclusive propofol anaesthesia in patients undergoing these procedures.

Methods We conducted a randomised, double-blinded controlled trial in adult patients scheduled to undergo thyroid and parathyroid surgery at two medical centres in mainland China. Patients were allocated randomly (1:1, stratified by sex and trial site) to an opioid-free anaesthesia group (esketamine, lidocaine, dexmedetomidine and propofol) or an opioid-inclusive group (sufentanil and propofol). Propofol infusions were titrated to bispectral index 45–55. Patients received prophylaxis for nausea and vomiting using dexamethasone and ondansetron and multimodal analgesia with paracetamol and flurbiprofen axetil. The primary outcome was the incidence of postoperative nausea and vomiting in the first 48 h after surgery.

Results We assessed 557 patients for eligibility and 394 completed this trial. The incidence of postoperative nausea and vomiting in the first postoperative 48 h was lower in the opioid-free anaesthesia group (10/197, 5%) compared with opioid-inclusive group (47/197, 24%) (OR (95%CI) 0.17 (0.08–0.35), $p < 0.001$), yielding a number needed to treat of 5.3. Additionally, opioid-free propofol anaesthesia was associated with a reduced need for rescue anti-emetics, lower rates of hypotension and desaturation after tracheal extubation, and higher patient satisfaction. Time to tracheal extubation was prolonged slightly in the opioid-free group. The two groups had similar postoperative pain scores and 30-day outcomes.

Discussion Opioid-free propofol anaesthesia reduced postoperative nausea and vomiting in patients undergoing thyroid and parathyroid surgery. An opioid-free anaesthetic regimen can optimise anaesthetic care during thyroid and parathyroid surgery.

Correspondence to: Ke Peng
Email: pengke0422@163.com
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Introduction

Postoperative nausea and vomiting (PONV) is a distressing complication in patients who undergo thyroid and parathyroid surgery, with an incidence ranging from 20% to 60% [1–3]. Female sex, not smoking, previous PONV or motion sickness history and opioid use are known risk factors as per the Apfel scoring system [4]. Postoperative nausea and vomiting are associated with worse patient outcomes, such as postoperative haemorrhage, delayed recovery after surgery, prolonged hospital stay and increased health service costs [5–8]. Despite anti-emetic prophylaxis, PONV remains a persistent problem for patients undergoing thyroid and parathyroid surgery.

Compared with inhalational anaesthesia, propofol anaesthesia helps to reduce PONV, while peri-operative administration of opioids increases the risk of PONV [4, 9, 10]. Data from meta-analysis suggests that traditional opioid-inclusive anaesthesia did not reduce postoperative pain but was associated with an increased rate of PONV [11]. As an alternative to opioid-inclusive anaesthesia, opioid-free anaesthesia provides anaesthesia and intra-operative analgesia using α2 agonists (clonidine or dexmedetomidine), N-methyl-d-aspartate antagonists (ketamine or esketamine), magnesium sulphate and local anaesthetics [12, 13]. It is not known whether the use of opioid-free anaesthesia in the setting of propofol anaesthesia and PONV prophylaxis decreases the rate of PONV or impacts on postoperative outcomes after thyroid and parathyroid surgery.

We aimed to test the hypothesis that opioid-free propofol anaesthesia vs. opioid-inclusive propofol anaesthesia would reduce the incidence of PONV in the first 48 h postoperatively for patients undergoing thyroid and parathyroid surgery. We also assessed postoperative pain, adverse events, patient satisfaction and 30-day outcomes.

Methods

We conducted a randomised, double-blinded controlled trial at two medical centres in Suzhou, China. The Institutional Review Board approved this trial and all patients provided written informed consent. The implementation of this trial followed CONSORT guidelines and was based on a published protocol [14]. The original protocol and statistical plan are available in online Supporting Information Appendix S1.

We enrolled adult patients who were ASA physical status 1–3 and undergoing thyroid and parathyroid surgery requiring general anaesthesia. We did not study patients with any dyspnoea or tracheal compression; formal diagnosis of obstructive sleep apnoea; biochemical hyperthyroidism or hypothyroidism (based on biochemistry); left ventricular ejection fraction < 40%; heart rate < 50 beats.min^{-1}; sick sinus syndrome or second-degree or greater atrioventricular block; Child-Pugh-Turcotte class C hepatic dysfunction; need for renal replacement therapy; seizures or epilepsy; chronic pain history; pre-operative use of sedatives or analgesics; pregnancy or breastfeeding; or allergy to medications used in this study.

An independent researcher generated the random sequence using an online tool with a 1:1 ratio, permuted blocks of 2 and 4 and stratification by sex and trial site. We used opaque sealed envelopes to conceal the random sequence. Shortly before surgery, a research nurse anaesthetist not involved in patient enrolment, peri-operative care or outcome assessment accessed the sequence and assigned patients to the opioid-free group or the opioid-inclusive group. To ensure blinding, this nurse anaesthetist prepared the study medications (esketamine, sufentanil, lidocaine, dexmedetomidine and normal saline placebo) in identical syringes labelled with medication numbers [14]; these solutions were indistinguishable visually. Patients, anaesthetists, other clinical staff, outcome assessors and statisticians remained blinded to group allocation until the final analysis.

Patients received standard monitoring. To induce anaesthesia, we administered intravenous propofol 1.5–2.0 mg.kg^{-1} to both groups of patients. Patients allocated to the opioid-free group received intravenous esketamine 0.3 mg.kg^{-1} and intravenous lidocaine 1 mg.kg^{-1}, while patients allocated to the opioid-inclusive group were given intravenous sufentanil 0.3 μg.kg^{-1} and normal saline volume matched to lidocaine. After induction, patients in the opioid-free group received dexmedetomidine infusion (0.5 μg.kg^{-1} followed by 0.2 μg.kg^{-1}.h^{-1} until skin closure) and those in the opioid-inclusive group received 0.9% saline infusion. After tracheal intubation with cisatracurium 0.15–0.2 mg.kg^{-1}, the patients' lungs were ventilated. During anaesthesia, propofol infusion was manually adjusted to maintain a bispectral index of 45–55. For intra-operative analgesia, patients received esketamine 0.1 mg.kg^{-1} boluses in the opioid-free group or sufentanil 0.1 μg.kg^{-1} boluses in the opioid-inclusive group. Cisatracurium was used only to facilitate tracheal intubation. Patients had a spontaneous neuromuscular recovery, and we did not routinely use pharmacological antagonism. If patients had residual neuromuscular blockade (train-of-four ratio < 0.9), intravenous neostigmine 1 mg and atropine 0.5 mg were administered. Tracheal extubation was performed in the

operating theatre and patients were transferred subsequently to a post-anaesthesia care unit (PACU).

For all patients, multimodal analgesia was prescribed and included oral paracetamol (500 mg 1 h before and every 6 h after surgery) and intravenous flurbiprofen axetil (50 mg intra-operatively and 50 mg twice daily) until 48 h postoperatively or hospital discharge. Rescue analgesia with intravenous tramadol 50 mg was given to treat postoperative pain with a score ≥ 4 on an 11-point numerical rating scale (0 = no pain and 10 = the most severe pain). Patients in both groups received routine prophylaxis against PONV with intravenous dexamethasone 5 mg on induction and ondansetron 4 mg intra-operatively. Additional intravenous ondansetron 4 mg was administered as a rescue anti-emetic if required.

Baseline blood pressure and heart rate were measured pre-operatively. Hypotension (mean blood pressure < 65 mmHg or a decrease in mean blood pressure > 30% of baseline); bradycardia (heart rate < 50 beats.min^{-1}); hypertension (increase in mean blood pressure > 30% of baseline); tachycardia (heart rate > 100 beats.min^{-1}); and desaturation (peripheral oxygen saturation < 95% on room air) were treated at the discretion of anaesthesia team. Other peri-operative care was based on institutional clinical standards.

We collected patient baseline data and calculated the Apfel PONV risk score for each patient [4]. We also estimated the risk of major adverse events according to the Cervical Endocrine Surgery Risk Index (CESRI) developed from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) [15]. Data on surgical characteristics, haemodynamic events and other peri-operative data were extracted from the electronic medical records and nursing notes.

The primary outcome was the occurrence of PONV (including episodes of nausea, retching and vomiting) within the first 48 h postoperatively. Nausea was defined as an unsettled feeling of having an urge to vomit, retching was defined as when gastric content was forced without vomitus expelled through the mouth, and vomiting was defined as a forceful expulsion of gastric content. The time of leaving the operating theatre was defined as `time 0´. Two experienced researchers blinded to the group assignment assessed PONV at PACU discharge and at 24 h and 48 h by ward visits or via telephone if patients were discharged from hospital.

Secondary outcomes included: severity of PONV, rated as mild (not interfering with basic activities of daily living such as hygiene, dressing and walking), moderate (interfering with activities of daily living at times) or severe (hardly undertaking activities of daily living or having three or more episodes of vomiting) [16]; need for rescue anti-emetics; pain intensity at rest and while coughing assessed using the numerical rating scale at PACU discharge, 24 h and 48 h after surgery; need for rescue analgesics; interventions for haemodynamic events; desaturation after tracheal extubation; dizziness, headache, nightmare or hallucination; time to tracheal extubation; duration of PACU and postoperative hospital stay; patient satisfaction, rated using a 5-point Likert scale (5 = very satisfied to 1 = very dissatisfied); and 30-day major complications according to the definitions on the ACS NSQIP (online Supporting Information Table S1) [15].

According to the literature, PONV episodes occur in 44% of patients who undergo thyroid and parathyroid surgery [1, 2, 17]. We hypothesised that the administration of opioid-free anaesthesia could reduce PONV incidence to 30% (an absolute reduction of 14%). To test this difference with $\alpha = 0.05$ and $\beta = 0.2$, this trial needed 183 patients in each group. To account for potential dropouts, we recruited a total of 400 patients (200 in each group). We used PASS 15.0 (NCSS, LCC, Kaysville, UT, USA) to calculate the sample size.

We performed modified intention-to-treat analyses including all patients who were allocated with primary outcome data available. Missing data were not imputed. Continuous variables were assessed for distribution using the Shapiro–Wilk test and compared using the independent t-test if distributed normally or the Mann–Whitney test if not. Categorical variables are presented as number (proportion) and were compared using Fisher's exact test or χ^2 test. The interventional effect of opioid-free vs. opioid-inclusive anaesthesia was analysed further using odds ratio (OR) or median difference with 95%CI. For the primary outcome of PONV, we conducted a prespecified analysis with a multivariable logistic regression model adjusting for sex, smoking status, PONV or motion sickness history and trial sites. Additionally, we performed prespecified subgroup analyses for sex, Apfel PONV risk scores and trial site. Statistical significance was defined as a two-sided p value < 0.05. For the secondary outcomes, we employed multiple comparison corrections using the Benjamin-Hochberg approach, with the significance level of a false discovery rate of q value < 0.05. We conducted statistical analyses using SPSS (version 19.0, IBM SPSS, Chicago, IL, USA).

Results

Between 10 May and 30 December 2022, a total of 400 patients were enrolled and allocated randomly (Fig. 1). Three patients did not undergo the scheduled surgical

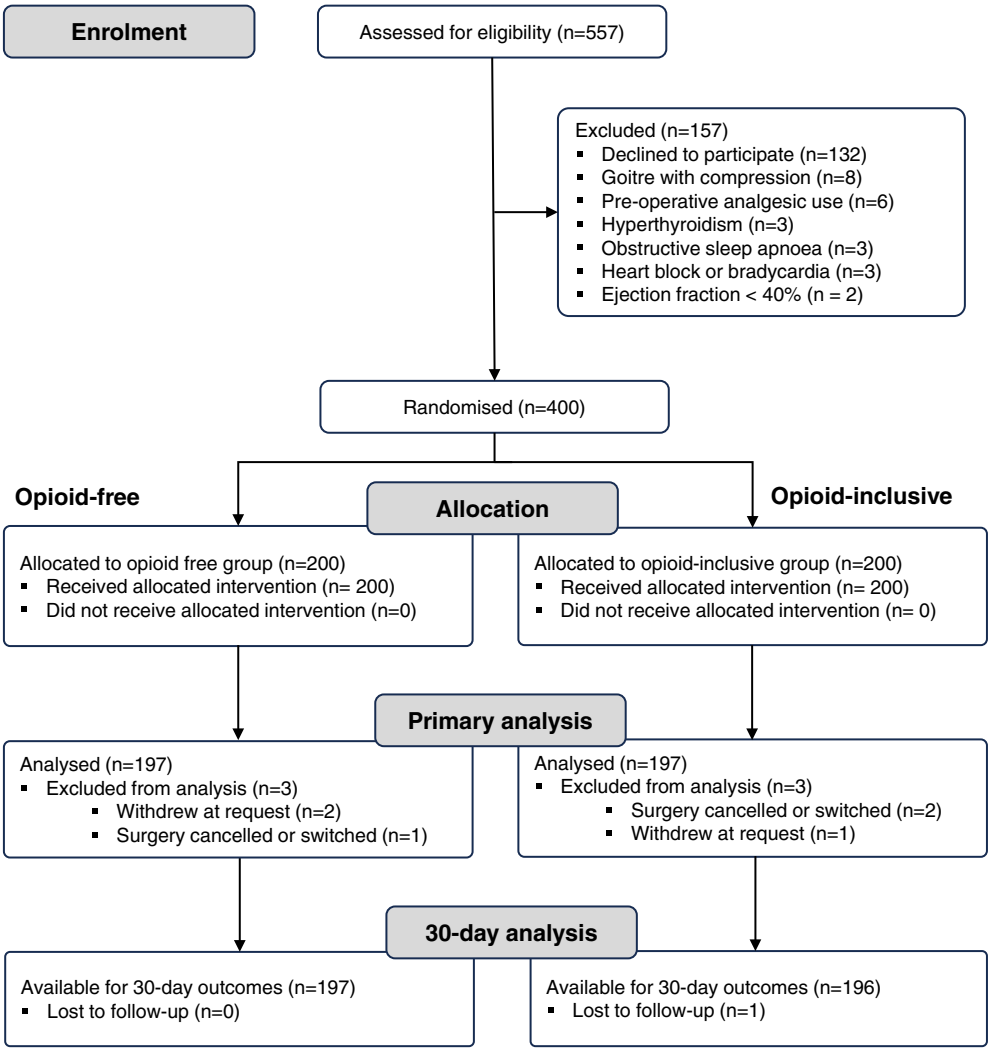

Figure 1 Study flow diagram.

procedures and three withdrew informed consent. Ultimately, 394 patients completed the trial and had primary outcome data available. One patient in the control group was lost to 30-day follow-up. Baseline characteristics were well balanced between the groups (Table 1). Intra-operative data were similar between groups excepting expected differences in the use of esketamine, dexmedetomidine, lidocaine and sufentanil (Table 1).

Postoperative nausea and vomiting occurred in 10/197 (5.1%) patients allocated to the opioid-free group, compared with 47 of 197 (23.9%) patients allocated to the opioid-inclusive group (risk difference -18.8%; OR (95%CI) 0.17 (0.08–0.35); number needed to treat 5.3; $p < 0.001$) (Table 2). In the adjusted analysis, patients allocated to opioid-free group still exhibited significantly lower odds of PONV (OR (95%CI) 0.16 (0.08–0.34) $p < 0.001$). Specifically, most PONV episodes occurred within 24 h postoperatively. The effects of opioid-free anaesthesia on PONV did not differ among the prespecified subgroups of sex, Apfel PONV risk scores or trial sites (Fig. 2).

Secondary outcomes are summarised in Table 3. During the first 24 h postoperatively, patients allocated to the opioid-free group showed reduced rates of mild and moderate-to-severe PONV. During 24–48 h postoperatively, 14 patients rated PONV as mild, all from the opioid-inclusive group. There was a reduced need for rescue anti-emetics in patients allocated to the opioid-free group. Pain scores were similar between the two groups without clinically significant differences. Patients allocated to the opioid-free group had reduced incidences of hypotension with intervention and desaturation after tracheal extubation. This group had a longer time to tracheal extubation, whereas the durations of PACU stay and postoperative hospital stay were similar between

Table 1 Baseline and peri-operative data of patients receiving an opioid-free or opioid-inclusive anaesthetic regimen. Values are mean (SD), number (proportion) or median (IQR [range]).

	Opioid-free n = 197	**Opioid-inclusive n = 197**
Age; y	45 (11.5)	46 (12.1)
Sex; female	160 (81%)	160 (81%)
Height; cm	163 (6.7)	163 (6.2)
Weight; kg	62 (9.5)	63 (8.6)
BMI; $kg.m^{-2}$	23 (2.8)	24 (2.6)
Current smoker	11 (6%)	14 (7%)
History of PONV or motion sickness	57 (29%)	61 (31%)
ASA physical status		
1	180 (91%)	177 (90%)
2	17 (9%)	20 (10%)
Pre-operative medications		
ACEI or ARB	11 (6%)	7 (4%)
β-blockers	3 (2%)	3 (2%)
Calcium channel blockers	13 (7%)	15 (8%)
Other	3 (2%)	3 (2%)
Apfel PONV risk score		
0	9 (5%)	12 (6%)
1	24 (12%)	22 (11%)
2	112 (57%)	109 (55%)
3	52 (26%)	54 (27%)
Total risk score	2 (2–3 [0–3])	2 (2–3 [0–3])
CESRI score		
0–14	96 (49%)	89 (45%)
15–19	85 (43%)	94 (48%)
20–24	16 (8%)	14 (7%)
Total risk score	15 (13–17 [13–22])	15 (13–17 [13–24])
Trial site		
Site 1	137 (70%)	136 (69%)
Site 2	60 (31%)	61 (31%)
Anaesthetics and analgesics		
Propofol; mg	740 (620–900 [400–1420])	690 (545–835 [330–1580])
Esketamine; mg	35 (30–40 [20–55])	–
Dexmedetomidine; μg	45 (40–53 [26–80])	–
Lidocaine; mg	61 (55–69 [42–100])	–
Sufentanil; μg	–	40 (35–45 [20–60])
Use of neostigmine/atropine	16 (8%)	18 (9%)
Surgical type		
Thyroid lobectomy	142 (72%)	141 (72%)
Total thyroidectomy	48 (24%)	48 (24%)
Thyroidectomy with neck dissection	7 (3%)	7 (4%)
Parathyroidectomy	0	1 (1%)
Pathology		
Benign	48 (24%)	49 (25%)
Malignant	149 (76%)	148 (75%)
Surgical time; h	1.2 (1.0–1.5 [0.5–2.8])	1.2 (0.01–1.5 [0.6–3.2])

PONV, postoperative nausea and vomiting; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CESRI, Cervical Endocrine Surgery Risk Index.

Table 2 Primary outcome of patients receiving opioid-free or opioid-inclusive anaesthetic regimen. Values are number (proportion).

	Opioid-free n = 197	Opioid-inclusive n = 197	Odds ratio (95%CI)	p value	Adjusted odds ratio (95%CI)*	Adjusted p value*
Primary outcome						
PONV 0–48 h	10 (5%)	47 (24%)	0.17 (0.08–0.35)	< 0.001	0.16 (0.08–0.34)	< 0.001
PONV within different periods						
In PACU	0	2 (1%)	0 (0–2.16)	–	–	–
0–24 h	10 (5%)	46 (24%)	0.18 (0.09–0.36)	–	–	–
24–48 h	0	14 (7%)	0 (0–0.25)	–	–	–

PONV, postoperative nausea and vomiting; PACU, post-anaesthesia care unit.
*Multivariable logistic regression adjusting for sex, smoking status, history of PONV or motion sickness, and trial sites.

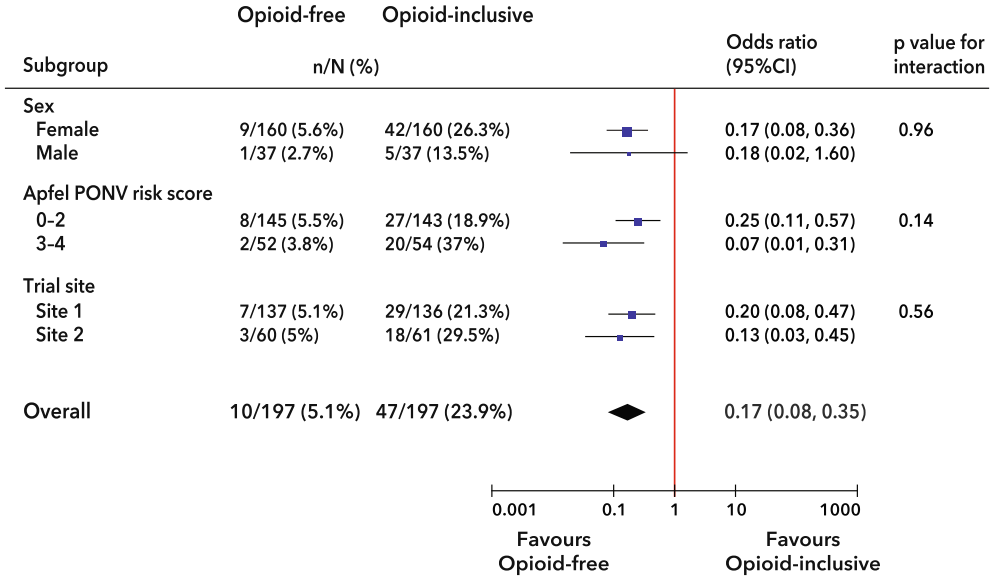

Figure 2 Subgroup analyses of postoperative nausea and vomiting (PONV) for patients receiving an opioid-free vs. opioid-inclusive anaesthetic regimen.

groups. Patients allocated to the opioid-free group showed higher satisfaction with anaesthesia and analgesia. Two patients allocated to the opioid-inclusive group underwent tracheal reintubation and re-operation within 30 days of surgery due to postoperative bleeding. While no patients allocated to the opioid-free group required a return to theatre, this difference was not significant.

Discussion

This randomised, double-blind controlled trial showed that opioid-free propofol anaesthesia significantly reduced the incidence of PONV during the first 48 h following thyroid and parathyroid surgery relative to opioid-inclusive propofol anaesthesia. Additionally, there was a reduced need for rescue anti-emetics, decreased rates of hypotension and desaturation after tracheal extubation and higher patient satisfaction in the opioid-free group. The time to tracheal extubation was slightly longer in patients allocated to the opioid-free group.

Opioids produce strong analgesia and have long been regarded as a cornerstone of peri-operative pain management [18]. However, opioids are associated with adverse effects such as PONV; respiratory depression; hyperalgesia; immunosuppression; gastrointestinal paralysis; delirium; and opioid dependence [19–22]. Many patients have their first opioid exposure in the peri-operative setting and can be expected to benefit from opioid-free anaesthesia techniques. Previously reported results of studies of opioid-free anaesthesia have delivered mixed results: some studies have shown that opioid-free

Table 3 Secondary outcomes of patients receiving an opioid-free or opioid-inclusive anaesthetic regimen. Values are number (proportion) or median (IQR [range]).

	Opioid-free n = 197	Opioid-inclusive n = 197	Odds ratio or median difference (95%CI)	p value	q value*
PONV severity in the PACU					
Mild	0	2 (1%)	0 (0–2.16)	0.499	0.594
PONV severity until 24 h					
Mild	9 (5%)	32 (16%)	0.25 (0.11–0.51)	< 0.001	< 0.001
Moderate	1 (1%)	8 (4%)	0.12 (0.01–0.79)	0.037	0.071
Severe	0	6 (3%)	0 (0–0.70)	0.030	0.063
PONV severity during 24–48 h					
Mild	0	14 (7%)	0 (0–0.25)	< 0.001	< 0.001
Need for rescue anti-emetics	2 (1%)	18 (9%)	0.10 (0.02–0.41)	< 0.001	0.001
Pain scores at rest					
PACU discharge	1 (0–1 [0–3])	1 (0–1 [0–3])	0 (0–0)	0.697	0.726
24 h	1 (0–1 [0–2])	1 (0–1 [0–4])	0 (0–0)	0.017	0.045
48 h	0 (0–1 [0–2])	0 (0–1 [0–3])	0 (0–0)	< 0.001	< 0.001
Pain scores while coughing					
PACU discharge	1 (0–2 [0–5])	1 (0–2 [0–4])	0 (0–0)	0.586	0.637
24 h	2 (1–2 [0–3])	2 (1–3 [0–5])	0 (0–0)	< 0.001	< 0.001
48 h	1 (0–1 [0–3])	1 (1–2 [0–3])	0 (0–0)	< 0.001	< 0.001
Need for rescue analgesics	1 (1%)	7 (4%)	0.14 (0.01–1.00)	0.068	0.121
Hypotension with intervention	1 (1%)	9 (5%)	0.11 (0.01–0.65)	0.020	0.045
Bradycardia with intervention	3 (2%)	10 (5%)	0.29 (0.08–1.00)	0.087	0.136
Hypertension with intervention	11 (6%)	6 (3%)	1.88 (0.68–5.10)	0.215	0.299
Tachycardia with intervention	9 (5%)	5 (3%)	1.84 (0.63–4.97)	0.276	0.345
Desaturation after extubation	1 (1%)	9 (5%)	0.11 (0.01–0.65)	0.020	0.045
Dizziness or headache	41 (21%)	39 (20%)	1.07 (0.65–1.72)	0.802	0.802
Nightmare or hallucination	7 (4%)	4 (2%)	1.78 (0.56–5.50)	0.543	0.617
Time to tracheal extubation; min	20 (15–25 [5–45])	15 (10–20 [5–40])	5 (2–5)	< 0.001	< 0.001
Duration of PACU stay; min	25 (20–30 [15–50])	30 (20–30 [10–45])	5 (0–0)	0.081	0.135
Duration of postoperative stay; d	2 (1–2 [1–4])	2 (1–2 [1–5])	0 (0–0)	0.131	0.193
Patient satisfaction	5 (5–5 [3–5])	4 (4–5 [3–5])	1 (0–0)	< 0.001	< 0.001
30-day major complications	0	2 (1%)†	0 (0–2.15)	0.248	0.326

PONV, postoperative nausea and vomiting; PACU, post-anaesthesia care unit.
*Multiple comparison correction using the Benjamini-Hochberg method.
†n = 196.

anaesthesia is associated with a decreased incidence of PONV and postoperative opioid requirements [23–25], whereas others suggest that opioid-free anaesthesia administration did not reduce PONV or improve pain outcomes, but may increase adverse events such as sedation and bradycardia [26, 27]. Recently, we showed that an opioid-free anaesthesia regimen with dexmedetomidine, esketamine and sevoflurane halved the incidence of PONV (from 32% to 15%, OR (95%CI) 0.38 (0.16–0.91), p = 0.031) after thoracoscopic lung surgery [28]. Nonetheless, data are limited for the use of opioid-free anaesthesia techniques in patients undergoing thyroid and parathyroid surgery.

The predicted incidence of PONV in patients allocated to the opioid-inclusive group was 44% [1, 2, 17]. However, we observed a lower PONV rate of 24% in this group. This reduction can be attributed to the use of propofol anaesthesia instead of inhalational anaesthesia and mandatory PONV prophylaxis for patients in both groups. A recent consensus guideline for PONV management recommends the use of multimodal prophylactic drugs including propofol anaesthesia and anti-emetic prophylaxis

[10]. By mandating induction and maintenance of anaesthesia with propofol, we avoided exaggerating the interventional effects of opioid-free anaesthesia and ensured the best clinical practice in the opioid-inclusive group.

Key strengths of our trial include the rigorous study design and implementation according to a pre-published protocol [14]. However, there are notable limitations. First, we conducted this trial at two medical centres in eastern China. Further studies are required to ascertain the generalisability of study results to patients in Western countries. Second, our patients had a low surgical risk. Approximately 90% of patients were ASA physical status 1, and both groups had a median CESRI score of 15. Lastly, our patients had a median Apfel PONV risk score of 2, representing a moderate risk of developing PONV. The effects of opioid-free anaesthesia for patients with higher PONV risk need to be evaluated in future studies.

In conclusion, the administration of opioid-free propofol anaesthesia reduced the incidence of PONV after thyroid and parathyroid surgery. Opioid-free anaesthesia also led to a reduced need for rescue anti-emetics, lower rates of hypotension and desaturation and higher patient satisfaction. While an increase in tracheal extubation time was observed in patients allocated to the opioid-free group, this was of limited clinical significance. This trial provides compelling evidence that an opioid-free anaesthesia regimen can be incorporated into individualised anaesthetic care and pain management for patients undergoing thyroid and parathyroid surgery with improved patient outcomes.

Acknowledgements

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Trial protocol and statistical plan.

Table S1. Definitions of major complications according to the National Surgical Quality Improvement Program from the American College of Surgeons.