Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Opioid-Free Anesthesia Improved the Quality of Recovery After Thyroidectomy Through Pre-Emptive and Preventive Analgesia: A Randomized Controlled Trial

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Background: Opioid-free anesthesia (OFA) is increasingly being adopted to provide effective analgesia and reduce opioid-related adverse events. However, existing literature on OFA remains contentious, and its impact on postoperative recovery following thyroidectomy has not been evaluated. Therefore, we examined the hypothesis that OFA enhances the early quality of recovery in patients undergoing thyroid surgery.

Methods: In this randomized controlled trial, 204 adult patients undergoing thyroidectomy were randomly assigned to receive either OFA (esketamine, dexmedetomidine, and bilateral superficial cervical plexus blocks) or opioid-based anesthesia (OBA, sufentanil and remifentanil). The primary outcome was the quality of recovery on the first postoperative day, assessed using the quality of recovery-15 scale. Secondary outcomes included sleep quality score, area under the curve of pain intensity. Anesthesia-related complications were also recorded.

Results: On the first postoperative day, the OFA group had a significantly higher quality of recovery-15 score versus the OBA group (137.6 [5.6] vs 128.2 [10.5], mean difference = 9.4, 95% CI, 7.0–11.7, $P < 0.001$). Patients in the OFA group also had better sleep quality (mean difference = 7.8, $P < 0.001$), lower area under the curve of pain intensity versus those in the OBA group. The incidence of postoperative nausea and vomiting was lower (1.0% vs 18.6%, $P < 0.001$) in the OFA group versus the OBA group. Patients receiving OFA had a delayed extubation and prolonged postanesthesia care unit stay.

Conclusion: We showed that with a pre-emptive and preventive analgesia effect, OFA improved quality of recovery, sleep quality, pain, and postoperative nausea and vomiting after thyroidectomy. However, a prolonged emergence recovery was observed when patients receiving OFA strategy, warranting further investigation to optimize agent design and monitoring method to balance the intraoperative anesthesia depth.

Name of Trial Registry: Chinese Clinical Trial Registry.

Registration Number: ChiCTR2300070794; URL: https://www.chictr.org.cn/showproj.html?proj=196152.

Plain Language Summary: Thyroid surgery is increasingly performed as day case procedures. With the goal of enhanced recovery, it is important to assess outcomes from the patient's perspective. This double blind, randomized controlled trial aimed to examine the effect of opioid-free anesthesia (OFA) on subjective quality of recovery (QoR) in patients undergoing thyroid surgery compared to those receiving opioid-based anesthesia. Importantly, we found that OFA improved QoR, sleep quality, pain, and postoperative nausea and vomiting after thyroid surgery, although it was associated with an increased risk of prolonged emergence recovery. Although cumulative effects of OFA has been shown to potentially enhance the overall postoperative QoR after different surgeries, such as orthopedic and thoracoscopic surgeries, our results showed that the advantages of OFA for QoR, particularly for thyroid surgery, remains limited and contentious. It warrants further investigation to optimize agent design of OFA.

Keywords: opioid-free anesthesia, dexmedetomidine, esketamine, quality of recovery, thyroid surgery

Received: 5 February 2025
Accepted: 26 May 2025
Published: 19 June 2025

Introduction

Thyroidectomies are well-defined procedures with low morbidity and mortality;[1] thus, the quality of recovery (QoR) has been becoming the focus of perioperative management. Anesthesia methods and potential adverse effects are important segments in the multifaceted process of postoperative recovery.[2,3] However, opioid-balanced anesthesia (OBA) usually leading to treatment-related side effects and risk of dependence and abuse,[4] which may delay the recovery after thyroid surgery. Studies have demonstrated that the analgesia and hemodynamic stability obtained with conventional opioids are achievable with adjunct medications and multimodal analgesic techniques.[5] Moreover, local anesthetic techniques and non-opioid analgesics, such as esketamine would provide a pre-emptive and preventive analgesia by blocking the afferent nociceptive volley and preventing central sensitization induced by noxious stimuli.[6,7] The cumulative effects of the benefits of opioid-free anesthesia (OFA) potentially enhance overall QoR after hysteroscopy and bariatric surgery.[8,9] However, literature supporting the advantages of OFA for QoR in thyroidectomies remains limited. Meanwhile, some studies suggested that OFA may also promote unwanted side effects.[10,11] It has been reported that bradycardia and delayed extubation occurred more in patients receiving OFA with dexmedetomidine.[10] Whether OFA is beneficial or harmful for enhanced recovery after thyroidectomies remains uncertain. Therefore, we designed an OFA strategy using intravenous esketamine and dexmedetomidine, combined with bilateral superficial cervical plexus blocks, as alternatives to OBA in thyroid surgery. We aimed to test the primary hypothesis that OFA may improve QoR, compared with OBA, on the first postoperative day in patients undergoing thyroidectomy. Secondary endpoints included postoperative pain, sleep quality, and incidence of complications.

Materials and Methods

Ethics and Study Design

This prospective randomized controlled trial was approved by the Ethics Committee of the Second Affiliated Hospital of Medical University (approval no.: YX2023-066) on 19 April 2023. This study complied with the Declaration of Helsinki and was prospectively registered in the Chinese Clinical Trial Registry (https://www.chictr.org.cn/showproj.html?proj=196152, registration no. ChiCTR2300070794) on 23 April 2023. Written informed consent was obtained from all the participants. The study reports complied with the consolidated standards of reporting Trials (CONSORT) criteria.[12]

Participants

Patients between 18 and 65 years of age, with American Society of Anesthesiologists physical status I–III scheduled for thyroid surgery were included in this study. We excluded patients with body mass index >35 kg m^{-2}, unstable ischemic cardiac disease, preoperative analgesic and sedative medication, uncontrolled hypertension (a supine systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg despite antihypertensive therapy), liver dysfunction (total bilirubin >1.5 times the upper limit of normal; or aspartate aminotransferase or alanine aminotransferase values ≥2x the upper limit of normal), kidney dysfunction (serum creatinine ≥2 mg dl^{-1}),[13] chronic pain, severe pulmonary hypertension, increased intracranial or intraocular pressure, psychiatric disorders, allergy to local anesthetics or analgesics, alcohol abuse, pregnancy, lactation, and re-operation.

Randomization and Blinding

The enrolled patients were randomly assigned in a 1:1 ratio to either the OBA or OFA group, which was created with SPSS (IBM, Armonk, NY, USA).[14] An assistant not involved in the study performed a blinded random allocation. The randomization list were concealed in sealed, opaque and consecutively numbered envelopes. An attending anesthesiologist (Dr. L. Z.), who did not participate in the following assessments, were informed about the study medication and provided the intraoperative monitoring and management. Thereafter, patients, surgeons, nurses, anesthesiologists aside from Dr. L. Z., investigators, and outcome assessors were blinded to the patients' group allocation.

Anesthesia and Perioperative Interventions

All patients were continuously monitored with blood pressure (BP), heart rate (HR), electrocardiogram, and oxygen saturation (SpO_2). Penehyclidine (0.5 mg) and dexamethasone (8 mg) were administered before anesthesia induction to

prevent glandular secretion and postoperative nausea and vomiting (PONV). Flurbiprofen (50 mg) was administered as a prophylactic analgesic after anesthesia induction.

Patients in the OFA group received dexmedetomidine at a loading dose of 0.75 μg kg^{-1} over 10 min before induction. Anesthesia was induced with intravenous midazolam (0.04 mg kg^{-1}), esketamine 0.5 mg kg^{-1}, propofol (1–2 mg kg^{-1}), and rocuronium (0.9 mg kg^{-1}). After intubation, the patient received a bilateral superficial cervical plexus block with 15 mL of 0.25% ropivacaine under the guidance of ultrasound. Anesthesia was maintained by continuous infusion of dexmedetomidine (0.5–1 μg kg^{-1} h^{-1}), esketamine (0.12 mg kg^{-1} h^{-1}), and propofol (4–6 mg kg^{-1} h^{-1}). Patients in the OBA group received intravenous midazolam (0.04 mg kg^{-1}), sufentanil (0.4 μg kg^{-1}), propofol (1–2 mg kg^{-1}), and rocuronium (0.9 mg kg^{-1}) for anesthesia induction and tracheal intubation. The neck skin was disinfected without nerve block performance. Anesthesia was maintained by a bolus of sufentanil (5–10 μg), continuous infusion of propofol (4–6 mg kg^{-1} h^{-1}) and remifentanil (0.1–0.2 μg kg^{-1} min^{-1}) (Figure 1). As a limitation of our study design, we did not use an objective and standard monitoring method to assess the anesthesia depth. It was assessed and adjusted according to the clinical evaluation by the attending anesthesiologist (Dr. L. Z.). At a proper depth of anesthesia, hypertension (defined as systolic BP >160 mmHg or elevation of >20% of baseline values for 1 min), hypotension (defined as systolic BP <90 mmHg or reduction of >20% of baseline values for 1 min), tachycardia (defined as HR > 100 bpm) and bradycardia (defined as HR < 50 bpm) were adjusted with urapidil, fluid therapy, ephedrine, phenylephrine, esmolol or atropine accordingly. The vasoactive agent dose was at the discretion of the anesthesiologist.

Post-surgery, the patients were transferred to the post-anesthesia care unit (PACU) after tracheal extubation. Sedation level and pain intensity were evaluated using the Richmond Agitation-Sedation Scale (RASS, with scores ranging from −5 [irresponsive and unarousable] to +4 [violent and combative], with 0 indicating calm and alert)[15] and numeric rating scale (NRS, an 11-point scale ranging from "0" [no pain] to "10" [worst pain]),[16] respectively. If patients requested additional pain relief or the NRS score was ≥4, pentazocine (10 mg) was administered for rescue analgesia. Additional oxygen was provided using a nasal cannula when pulse oxygen saturation <94% in room air. Droperidol rescue (0.5 mg) was administered to treat PONV. Patients were monitored for at least 30 min in the PACU and until they met the modified Aldrete score was ≥9.[17] In the ward, if the patient required pain relief, diclofenac sodium was provided.

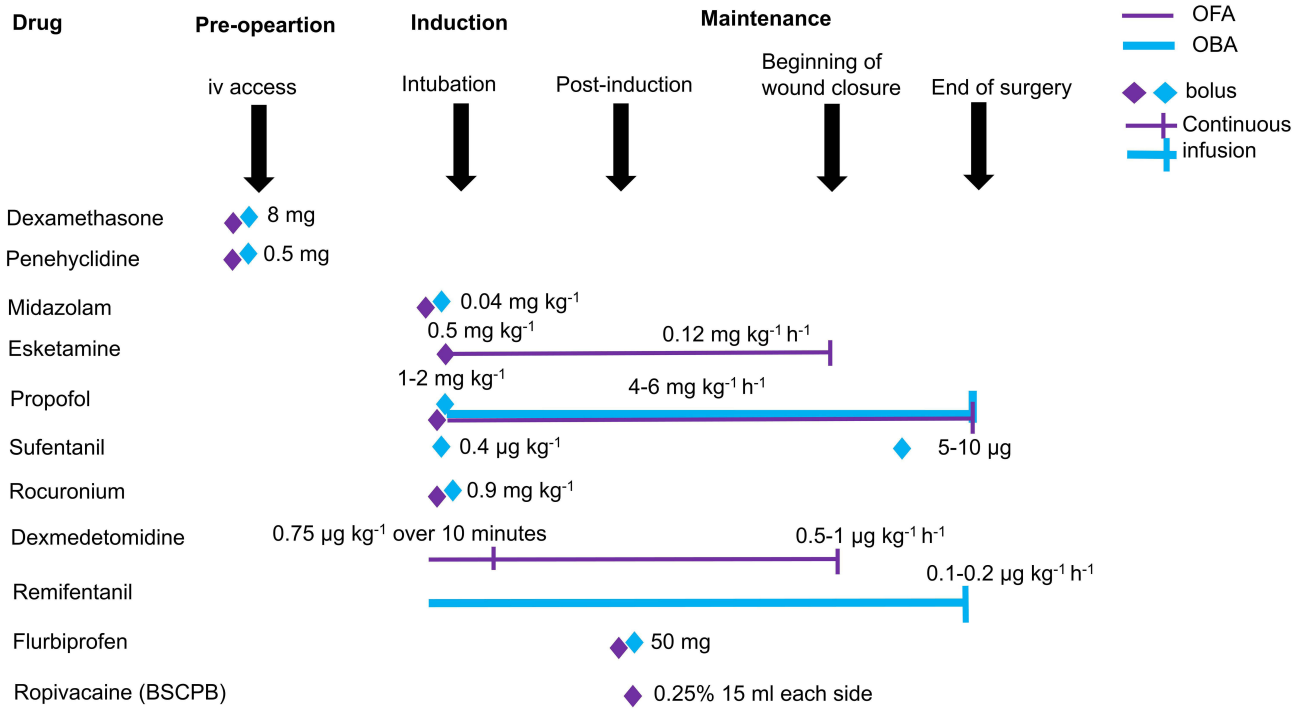

Figure 1 The strategies of two types of anesthesia.
Abbreviations: OFA, opioid-free anesthesia; OBA, opioid-based anesthesia; BSCPB, bilateral superficial cervical plexus block.

https://doi.org/10.2147/DDDT.S520856

Study Outcomes

Baseline data included patient characteristics, nature of work, degree of education, marital status, ASA physical status, New York Heart Association (NYHA) physical status, surgical history, preoperative comorbidities, ward capacity, lifetime alcohol consumption, and smoking index (Supplementary Methods 1 and 2).[18] Intraoperative data included surgical hours, surgery type, dosage of anesthetics, fluid infusion, surgery duration, BP, and HR.

The primary outcome of the QoR was evaluated using the QoR-15 questionnaire score, consisting of 15 common postoperative questions across five dimensions of health: patient support, comfort, emotions, physical independence and pain. The maximum score achievable is 150 with a potential minimum score of 0. Higher scores indicate a higher quality of recovery experience (Supplementary Methods 3)[19] on the first postoperative day. The second outcomes included subjective sleep quality on the night of surgery, which was evaluated using the Richards–Campbell Sleep Questionnaire (RCSQ) (Supplementary Methods 4);[20] NRS pain scores within 24 h postoperatively; intraoperative BP and HR values; incidence and consumption of intraoperative vasoactive drug; time to tracheal extubation; RASS scores in PACU; length of PACU stay; incidence of rescue analgesia, time to first administration of rescue analgesic; and days of hospitalization post-surgery. Biochemical outcomes included postoperative levels of cortisol and C-reactive protein in the saliva samples. Incidence of anesthesia-related complications, including intraoperative awareness, postoperative diplopia, hallucinations, nightmares, dizziness, oxygen desaturation,[21] and PONV (Supplementary Methods 5), were recorded.[22] At 30 and 90 d after surgery, patients were followed up by phone interviews for QoR-15 and pain NRS scores.

Statistical Analysis

Based on a previous study, the established minimum clinically important difference in the QoR-15 score after surgery was 8.0.[23] We selected a standard deviation (SD) of 18 for the study population and calculated the sample size by using PASS (NCSS, Kaysville, UT, USA) for Windows. Power analysis on the assumption of a type I error of 0.05 and a power of 0.80 to detect a significant difference in the mean QoR-15 scores, 81 patients were required for each group. To account for a possible 20% dropout rate, 204 patients were planned to be recruited in this study.

We assessed the inter-group balance of baseline data by using the absolute standardized difference (means, medians or proportions difference divided by the pooled SD). Baseline variables with an absolute standardized difference >0.3 were considered imbalanced.[24] Statistical analyses were performed using SPSS (IBM Corp., Armonk, NY, USA) and GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). The normality of the data distribution was tested by Shapiro–Wilk test and visual inspection of histograms. Continuous variables were presented as mean (SD) or median (interquartile range). Continuous variables with normal or approximately normal distribution were compared between the two groups by independent-samples test. Ordinal variables or data without normal distribution were analyzed with the Mann–Whitney comparison. Binary comparisons of the QoR-15 and RCSQ scores within groups were analyzed with paired *t*-test. Categorical variables are expressed as numbers (percentages), and were analyzed using chi-squared or Fisher's exact tests, as appropriate. The treatment effects of OFA and OBA were assessed using the mean, median difference, or relative risk with a 95% confidence interval (CI). Prespecified subgroup analyses of the QoR-15 score were conducted according to sex, age, nature of work, degree of education, marital status, and type of surgery.

The effects of interventions on the outcomes of hemodynamic parameters over time were analyzed with a linear mixed model. The RASS parameters over time were analyzed with a generalized estimating equations. When significant interactions were observed between the group, time, and group-by-time variables, post hoc analysis with Bonferroni correction was performed to adjust for multiple comparisons.[25] To summarize and compare NRS scores over time, the area under the curve (AUC) of the NRS score (AUC_{NRS}) was calculated using the trapezoidal rule. The Mann–Whitney *U*-test was used to compare the AUC_{NRS} scores between the groups. The time to the first rescue analgesia was analyzed using Kaplan–Meier survival analysis, followed by a Log rank test. For the secondary outcomes, a false discovery rate was applied to adjust for multiple testing correction based on the Benjamini-Hochberg method. We did not perform interim analysis or missing data imputation. For each hypothesis, assessments were 2-sided, and $P < 0.05$ were denoted statistically significant.

Results

Between May 2023 and February 2024, 214 patients were assessed for eligibility. Of these, 10 patients were excluded, and 204 patients underwent randomization. Primary outcome data were available for all patients. The statistical power is 88%. However, 72 patients failed to provide saliva samples due to xerostomia. The final follow-up was performed on 7 May 2024, and the 90-day outcome data was missing in three patients because of loss to follow-up (Figure 2).

The baseline characteristics, total QoR-15 and RCSQ scores were well balanced between the two groups. The propofol requirement was significantly higher in the OFA group versus the OBA group (4.7 [0.8] vs 5.0 [0.7] mg kg^{-1} h^{-1}, P=0.006). Other intraoperative data were comparable between the OBA and OFA groups (Table 1).

All patients reported a reduction in the total QoR-15 score on the first postoperative day compared with the baseline value ($P_{paired} < 0.001$). However, the OFA group exhibited a significantly higher total QoR-15 score, compared with the OBA group (OBA: 128.2 [10.5] vs OFA: 137.6 [5.6], mean difference = 9.4, 95% CI, 7.0–11.7, $P < 0.001$) (Table 2). Specifically, the OFA group patients experienced significantly improved recovery in physical comfort, emotional state, and pain ($P < 0.001$; $P < 0.001$; $P = 0.005$) (Table S1). The responses by item according to the intervention are represented in the radar plot of QoR-15 in Figure S1. The treatment effects of OFA and OBA significantly differed in the subgroups based on sex, age, degree of education, and type of surgery (Figure S2).

The OFA group patients also exhibited a significantly higher RCSQ score, compared with the OBA group patients on the night of surgery (OBA: 20.4 [9.1] vs OFA: 28.2 [6.3], $P < 0.001$). The time to tracheal extubation and the length of

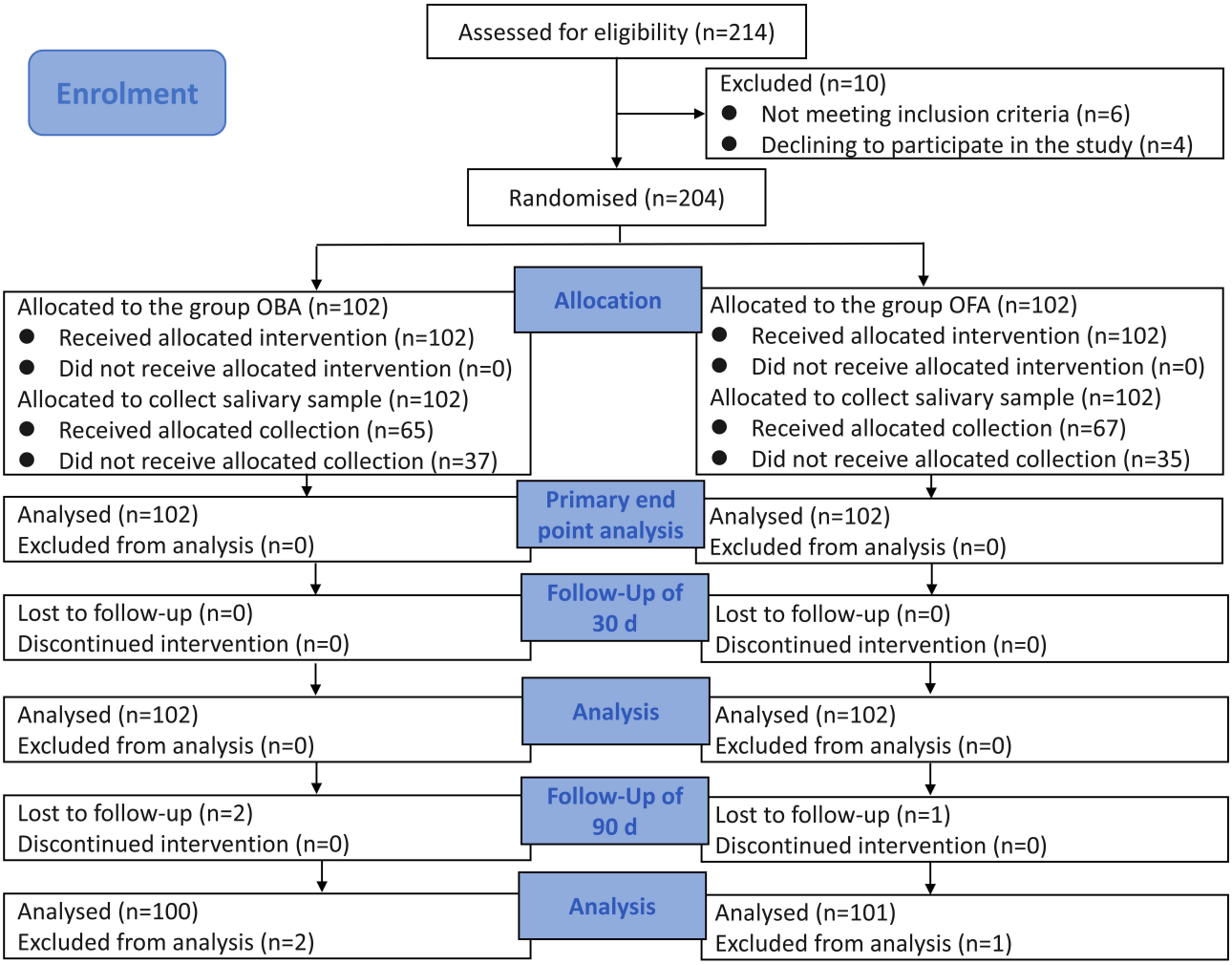

Figure 2 Trial flow diagram.
Abbreviations: OFA, opioid-free anesthesia; OBA, opioid-based anesthesia.

https://doi.org/10.2147/DDDT.S520856

Table 1 Baseline and Intraoperative Data of Patients in the OBA and OFA Group

	OBA Group (n = 102)	OFA Group (n = 102)	ASD	*P*
Age, y	44.6 (11.0)	45.0 (10.9)	0.05	0.779
Body mass index, kg m^{-2}	24.2 (3.2)	24.3 (2.7)	0.03	0.948
Sex			0.02	0.868
Male	24 (23.5)	23 (22.5)		
Female	78 (76.5)	79 (77.5)		
Nature of work			0.29	0.300
Unemployed	44 (43.1)	44 (43.1)		
Public enterprise	24 (23.5)	15 (14.7)		
Private enterprise	27 (26.5)	31 (30.4)		
Self-employment	7 (6.9)	12 (11.8)		
Degree of education			0.18	0.719
Primary school and below	34 (33.3)	32 (31.4)		
Middle school	30 (29.4)	30 (29.4)		
High school	20 (19.6)	26 (25.5)		
College and above	18 (17.6)	14 (13.7)		
Marital status			0.06	1.000
Married	95 (93.1)	96 (94.1)		
Unmarried	6 (5.9)	5 (4.9)		
Divorce	1 (1.0)	1 (1.0)		
ASA physical status			0.06	0.661
I	64 (62.7)	67 (65.7)		
II	38 (37.3)	35 (34.3)		
NYHA physical status			0.06	1.000
I	99 (97.1)	100 (98.0)		
II	3 (2.9)	2 (2.0)		
Preoperative comorbidities				
Hypertension	19 (18.6)	18 (17.6)	0.03	0.856
Diabetes	7 (6.9)	5 (4.9)	0.09	0.552
Chronic bronchitis	1 (1.0)	1 (1.0)	0	1.000
Surgical history				0.541
No	61 (59.8)	61 (59.8)	0	
Gynecology	12 (11.8)	10 (9.8)	0.10	
Obstetrics	16 (15.7)	11 (10.8)	0.07	
General surgery	10 (9.8)	13 (12.7)	0.09	
Orthopedics	3 (2.9)	7 (6.9)	0.19	
Ward capacity			0.16	0.263
Twin room	54 (52.9)	46 (45.1)		
Triple room	48 (47.1)	56 (54.9)		
Lifetime alcohol consumption			0.11	0.851
Never	83 (81.4)	86 (84.3)		
Moderate	18 (17.6)	15 (14.7)		
High-moderate	1 (1.0)	1 (1.0)		
Heavy	0 (0.0)	0 (0.0)		
Smoking index, pack · y	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.03	0.830
Preop total QoR-15	142.8 (4.4)	142.5 (4.7)	0.07	0.643
Preop total RCSQ	35.4 (7.7)	34.3 (7.9)	0.14	0.319
Surgical hours			0.30	0.178
8:00–12:00	34 (33.3)	44 (43.1)		
12:00–16:00	49 (48.0)	47 (46.1)		
16:00–20:00	19 (18.6)	11 (10.8)		

(*Continued*)

Table 1 (Continued).

	OBA Group (n = 102)	OFA Group (n = 102)	ASD	*P*
Type of surgery			0.19	0.491
Unilateral thyroidectomy + lymph node dissection	70 (68.6)	73 (71.6)		
Bilateral thyroidectomy + lymph node dissection	21 (20.6)	15 (14.7)		
Thyroidectomy	11 (10.8)	14 (13.7)		
Fluid infusion, mL	469.4 (203.0)	489.7 (163.1)	0.11	0.432
Duration of surgery, min	107.5 (48.3)	104.9 (41.4)	0.06	0.680
Sufentanil, μg kg^{-1}	0.5 (0.1)	0.0	7.04	NA
Remifentanil, μg kg^{-1} min^{-1}	0.1 (0.0)	0.0	NA	NA
Dexmedetomidine, μg kg^{-1} h^{-1}	0.0	0.7 (0.1)	0.99	NA
Esketamine, mg kg^{-1} h^{-1}	0.0	0.1 (0.0)	NA	NA
Propofol, mg kg^{-1} h^{-1}	4.7 (0.8)	5.0 (0.7)	0.40	0.006

Notes: Data are expressed as mean (SD) or n (%). An absolute standardized differences > 0.3 is considered imbalanced between the two groups.
Abbreviations: ASA, American society of anesthesiology; NYHA, New York Heart Association; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia; ASD, absolute standardized differences.

Table 2 Postoperative Data of Patients in the OBA and OFA Group

	OBA Group (n = 102)	OFA Group (n = 102)	Mean/Median Difference/RR (95% CI)	*P*
Total QoR-15 on POD1	128.2 (10.5)	137.6 (5.6)	9.4 (7.0, 11.7)	< 0.001
Total RCSQ on POD 1	20.4 (9.1)	28.2 (6.3)	7.8 (5.7, 10.0)	< 0.001
Time to extubation, min	6.5 (3.8)	10.8 (6.7)	4.3 (2.8, 5.8)	< 0.001
RASS score				
Arriving at PACU	0 (0.0, 0.0)	−1 (0.0, −1.0)	1 (1.0, 1.0)	< 0.001
10 min in PACU	0 (0.0, 0.0)	0 (0.0, −1.0)	0 (0.0, 0.0)	< 0.001
20 min in PACU	0 (0.0, 0.0)	0 (0.0, 0.0)	0 (0.0, 0.0)	< 0.001
30 min in PACU	0 (0.0, 0.0)	0 (0.0, 0.0)	0 (0.0, 0.0)	< 0.001
Length of PACU stay, min	30.0 (30.0, 30.0)	30.0 (45.0, 30.0)	0 (0.0, 0.0)	< 0.001
Patients requiring rescue analgesia	6 (5.9)	0 (0.0)	NA	0.038
PONV				
Incidence	19 (18.6)	1 (1.0)	19.0 (2.6, 139.3)	< 0.001
Score	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	< 0.001
Psychotomimetic side effects	31 (30.4)	20 (19.6)	1.6 (1.0, 2.5)	0.075
Dizziness	30 (29.4)	20 (19.6)	1.5 (0.9, 2.5)	0.104
Nightmares	0 (0.0)	0 (0.0)	NA	NA
Diplopia	0 (0.0)	2 (2.0)	NA	0.241
Hallucinations	1 (1.0)	3 (2.9)	0.3 (0.0, 3.2)	0.621
Oxygen desaturation	0 (0.0)	0 (0.0)	NA	NA
Length of hospital stay after surgery, d	4.0 (5.0, 3.0)	4.0 (5.0, 3.0)	0 (0.0, 0.0)	0.696

Notes: Data are expressed as mean (SD), median (interquartile range) or n (%). *P* values are from independent-sample *t*-tests, $P < 0.05$ indicates statistically significant differences between groups.
Abbreviations: OBA, opioid-based anesthesia; OFA, opioid-free anesthesia; RCSQ, Richards-Campbell sleep questionnaire; QoR-15, quality of recovery-15; Preop, preoperative; POD, postoperative day; CI, confidence interval; RASS, Richmond agitation-sedation scale; PACU, post anesthesia care unit; PONV, postoperative nausea and vomiting; RR, relative risk.

PACU stay were significantly longer, and the sedation levels in the PACU were significantly deeper in the OFA group than in the OBA group ($P < 0.001$). Significantly more patients received rescue analgesia in the OBA group than in the OFA group ($P = 0.038$). The incidence and scale scores of PONV were significantly lower in the OFA than in the OBA group ($P < 0.001$). Other side effects were comparable between groups. The length of hospitalization post-surgery was comparable between the two groups (Table 2). None of the patients reported intraoperative awareness.

The OFA group patients experienced less pain and exhibited lower AUC_{NRS} of pain intensity within postoperative 24 h than the OBA group patients (Figure 3). The time to first rescue analgesia was longer in the OFA versus the OBA group (Figure S3). The intraoperative BP and HR were significantly higher in the OFA versus the OBA group (Figure S4). Multiple testing correction for secondary outcomes were summarized in Table S2. As a limitation, the data for cortisol and C-reactive protein levels were not full sample sized (n = 65 in the OBA group vs n = 67 in the OFA group). When analyzed the collected samples, we found that the cortisol and C-reactive protein levels were comparable between the groups preoperatively, and significantly increased post-surgery in both groups. However, no significant differences were observed between the two groups postoperatively (Figure S5). The QoR-15 and pain NRS scores were similar at 30 and 90 days postoperatively (Table S3).

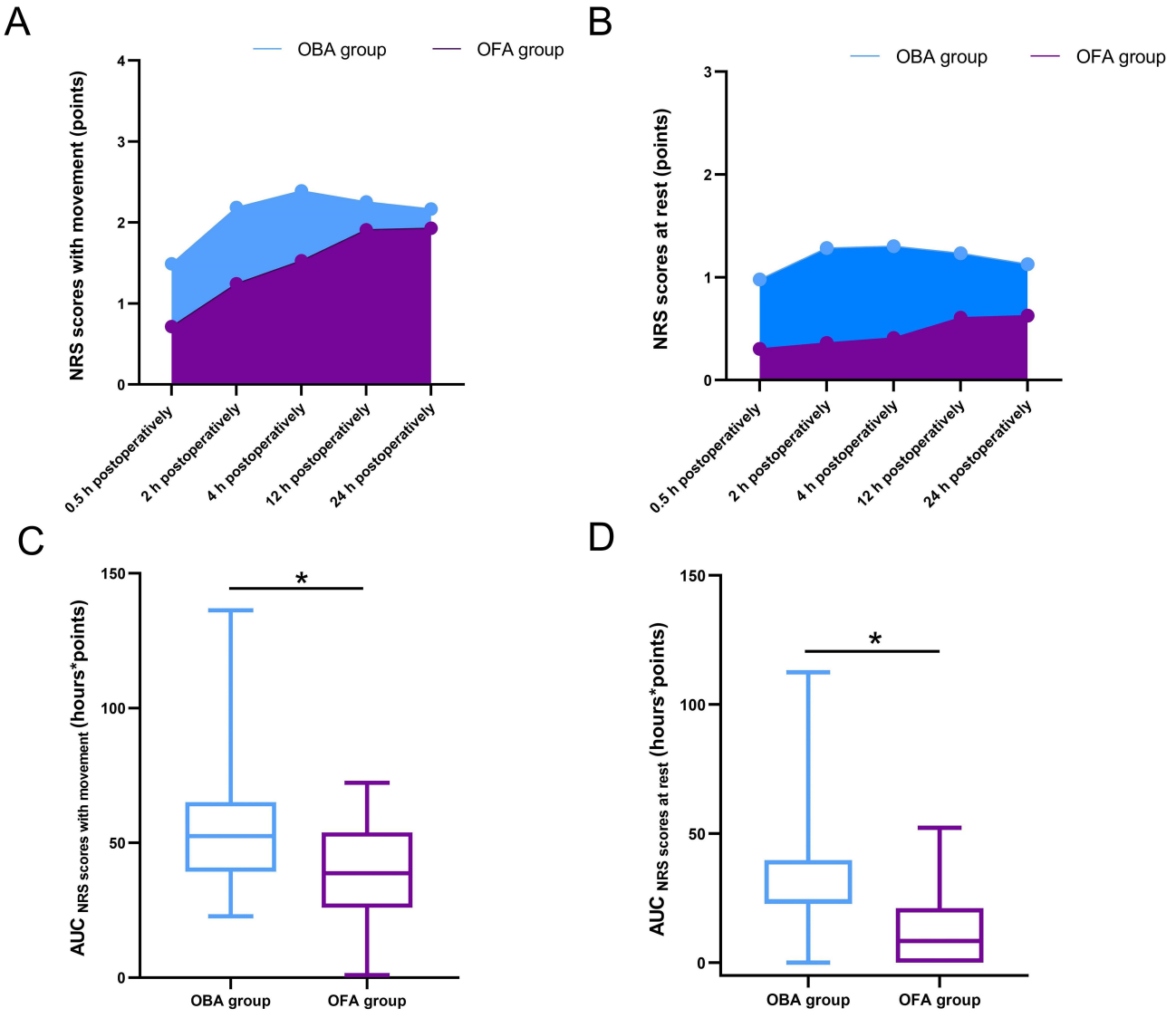

Figure 3 AUC of NRS scores with movement (**A** and **C**) and at rest (**B** and **D**) during the first 24 h after surgery in the study groups. AUC of the NRS scores were calculated using the trapezoidal rule (**A** and **B**). AUC data are expressed as the median (horizontal bar), interquartile range (box), and maximum and minimum values (whiskers). Comparisons between groups were performed using the Mann–Whitney *U*-Test (**C** and **D**). The asterisk (*) indicates statistically significant differences between groups ($P < 0.05$).

Abbreviations: OBA, opioid-based anesthesia; OFA, opioid-free anesthesia; NRS, numeric rating scale; AUC, area under the curve.

Discussion

Our results showed that the OFA strategy improved QoR, especially in the domains of physical comfort, emotional state, and pain management, on the first postoperative day in patients undergoing thyroidectomies. The OFA strategy also improved sleep quality and PONV without increasing psychiatric symptoms 24 h post-surgery. However, compared with OBA, this OFA strategy was associated with a prolonged emergence recovery and higher intraoperative BP.

Thyroidectomies are increasingly performed as day case procedures.[26] With the goal of enhanced recovery, it is important to assess outcomes from the patient's perspective.[2] The QoR-15 has been demonstrated to be a valid, reliable, and feasible outcome measure for surgeries and anesthesia protocols.[27] As shown in our study, patients usually exhibit a preoperative QoR-15 score lower than 150, which might be linked to patients' fatigue and anxiety. The QoR scores decreased further after surgery. However, the OFA strategy helped to elevate the total QoR-15 score by 9.8 points, compared with OBA. This value is not only statistically significant but also clinically significant.[28] From this perspective, QoR supports the use of OFA as the main anesthetic strategy for thyroidectomy.

In the OFA protocol, we performed a regional nerve block before the incision, aiming to block the afferent nociceptive volley and prevent central sensitization with pre-emptive analgesia.[29] We also chose alpha2-agonists and N-methyl-D-aspartic acid (NMDA) receptor antagonists, owing to the considerable analgesic potency and antianxiety effects.[30] Moreover, with a high affinity for NMDA receptors, esketamine would decrease the likelihood of central sensitization. The beneficial effect of esketamine would persist beyond the pharmacologic action of the drug, thus providing preventive analgesia.[6,7] Compared with OBA, OFA with dexmedetomidine and ketamine or esketamine can significantly reduce postoperative opioid consumption and incidence of PONV in multiple surgeries.[31–33] Consistent with these results, we further provide evidence that OFA with dexmedetomidine and esketamine improved postoperative pain and PONV when compared with OBA in thyroid surgery. Moreover, patients receiving OFA exhibited a higher postoperative sleep quality. This might owing to the effect of esketamine and dexmedetomidine. We previously demonstrated that esketamine improved sleep quality with OBA.[34] Qiu et al also reported that intraoperative esketamine infusion prevented sleep disturbance after gynecological surgery.[35] Studies have suggested that esketamine can prolong the average deep sleep duration and modulate circadian rhythms by regulating clock genes.[36] Additionally, dexmedetomidine might play a synergistic role as an integral part of the neuronal pathways of natural sleep.[37] Given the significant impact of pain, PONV, anxiety, and sleep on recovery, improvement in these clinical outcomes with OFA would contribute to higher scores in the QoR-15. Conversely, Massoth et al reported OFA did not improve pain and PONV during gynecological laparoscopy.[38] A possible explanation for this contradiction may be the difference of population. Female patients are more vulnerable to PONV owing to the effect of oestrogen on serotonin pathways.[39] Thus, further research is required to clarify the effects of OFA on patient populations and surgical procedures in terms of QoR.

Evidence of the hemodynamic stability of OFA remains controversial. Beloeil et al showed that OFA led to bradycardia, with an infusion rate of dexmedetomidine at 1.2 μg kg^{-1} h^{-1}.[10] In our study, the infusion rate of dexmedetomidine was 0.7 μg kg^{-1} h^{-1}, which could potentially reduce bradycardia risk. Consistent with Feng et al and Yan et al's studies,[31,32] the OFA group patients exhibited higher BP and required more antihypertensive drug intraoperatively. To rule out the insufficiency of anti-stress, Yan et al tested the blood glucose and demonstrated a comparable value between the OFA and OBA groups.[31] Similarly, we found no significant differences in the cortisol and C-reactive protein levels between the groups, though the saliva specimens were not collected from all the included participants. Since the elevations of blood glucose, cortisol and C-reactive protein levels are associated with stress, we hypothesized that the increase in BP might be due to sympathetic activation of esketamine and not the insufficiency of anti-stress.[40] However, without an objective monitoring method and full sample size of biochemical parameters, we were not sure the exact depth of anesthesia, which might impact the reliability of the hemodynamic outcomes.

Esketamine has a higher affinity for receptors than ketamine. It may bind more to NMDA receptors in the dorsal horn of the spinal cord rather than in the brain.[41] This may have reduced high risk of psychotomimetic effects in the OFA group. However, patients receiving OFA exhibited a deeper sedation and prolonged emergence recovery after surgery. Similarly, Feng et al and Beloeil et al found that OFA delayed extubation and prolonged PACU stay.[10,32] Feng et al attributed these findings to the sedative effect of dexmedetomidine.[32] Moreover, we observed that patients receiving OFA consumed more propofol. This phenomenon might potentially attributed to the elevated intraoperative BP, which likely

prompted the anesthesiologist to increase the propofol dosage, contributing to the prolonged emergence recovery. However, the interpretations warrant cautions and are only hypotheses, as there was no objective data supporting the depth of anesthesia in our study.

This study has some limitations. First, we realized that the major one is the anesthesia depth assessment. It was assessed based on clinical evaluation other than an objective monitoring method. Because esketamine activates the θ, δ, and γ waves of the cerebral cortex, which may be related to the acquisition of excited electroencephalography (EEG).[42,43] While propofol and benzodiazepines act on α and γ waves of the EEG and inhibit excitatory neurons. This indicates that the sedative monitoring values may be different in OFA and OBA. Objectively measuring the anesthesia depth produced by different sedatives and analgesics is a worthy topic for further exploration. We will utilize proper objective monitoring method to guide anesthesia depth in future prospective work. Second, the type and dosage of OFA agents originated from previous literature and our clinical practice; we acknowledge that it was not optimal. Further studies, particularly multicentre clinical studies, are required for optimization. Third, we assessed the early QoR only on the first postoperative day. Time points such as postoperative 48 and 72 h should be monitored for further analysis. Fourth, the saliva samples were not collected from the full sample of patients. This might weaken the analysis power. A larger sample size is required to determine the inflammation and stress response mechanisms that contribute to QoR. Fifth, to safeguard against catastrophic complications of postoperative bleeding and recurrent laryngeal nerve injury, patients are usually monitored for ≥72 h after thyroidectomy in our clinical practice. Thus, the length of hospitalization did not totally depend on the intervention of our study design.

Conclusions

In summary, we showed that the OFA strategy improved QoR on the first postoperative day in patients undergoing thyroid surgery. This might be associated with the pre-emptive and preventive analgesia effects, improved sleep quality and decreased risk of PONV. However, a prolonged emergence recovery was observed when patients receiving OFA strategy, warranting further investigation to optimize agent design and monitoring method to balance the intraoperative anesthesia depth.

Abbreviations

ASA, American Society of Anesthesiology; ASD, absolute standardized differences; AUC, area under the curve; BP, blood pressure; CI, confidence interval; EEG, electroencephalography; HR, heart rate; NMDA, N-methyl-D-aspartic acid receptor; NRS, numeric rating scale; NYHA, New York Heart Association; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting; QoR, quality of recovery; RCSQ, Richards–Campbell sleep questionnaire; RASS, Richmond agitation-sedation scale; SD, standard deviation; SpO_2, oxygen saturation.

Data Sharing Statement

Data is available on Mendeley at: https://data.mendeley.com/datasets/h5mhswsnsc/1, or from the corresponding author by Email wuyunanyi@163.com.

Ethics Approval and Informed Consent

This prospective randomized controlled trial was approved by the Ethics Committee of the Second Affiliated Hospital of Medical University (approval no.: YX2023-066) on 19 April 2023. This study complied with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Consent for Publication

The authors confirm that the details of any images, videos, recordings, etc can be published, and that the persons providing consent have been shown the article contents to be published.

Acknowledgments

The authors thank all study participants for their involvement in the study. We acknowledge the nurses for their excellent work of patient organization and nursing assistance.

Funding

This study was funded by Natural Science Foundation of Anhui Province (grant number: 2308085Y42 to YW), University Natural Science Research Project of Anhui Province (grant number: 2023AH053158 to YW), Anhui Province Quality Engineering Teaching Research Project (grant number: jyxm1149 to YW) and Translational Project of Clinical Medical Research of Anhui Province (grant number: 202304295107020017 to YW).

Disclosure

The authors report no conflicts of interest in this work.

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