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Original Contribution

Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial

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ABSTRACT

Study objective: The quality of recovery (QoR) of remimazolam-based and propofol-based total intravenous anesthesia was compared as measured by QoR-15 scores.
Design: A prospective, double-blind, randomized controlled, non-inferiority trial.
Setting: An operating room, a post-anesthesia care unit (PACU), and a hospital ward.
Patients: Female patients ($n = 140$; 20–65 years) scheduled for open thyroidectomy were enrolled and randomly assigned to the remimazolam or propofol group.
Interventions: The remimazolam group received continuous remimazolam infusions and effect-site target-controlled remifentanil infusions. The propofol group received effect-site target-controlled infusions of propofol and remifentanil.
Measurements: The primary outcome was QoR-15 on postoperative day 1 (POD1). The mean difference between the groups was compared against a non-inferiority margin of −8. Secondary outcomes were QoR-15 on POD2, hemodynamic data, time to lose and recover consciousness, sedation score upon PACU admission, pain, and postoperative nausea and vomiting profiles at the PACU and ward. Group-time interaction effects in hemodynamic data and QoR-15 were analyzed using a linear mixed model.
Main results: The total QoR-15 score on POD1 in the remimazolam group was non-inferior to that in the propofol group (mean [SD] 111.2 [18.8] vs. 109.1 [18.9]; mean difference [95% CI] 2.1 [−4.2, 8.5]; $p = 0.002$ for non-inferiority). The QoR-15 score on POD2 was comparable between the groups, and no group-time interaction was observed. At the end of anesthesia, after extubation, and upon arrival at the PACU, mean arterial pressure was significantly higher in the remimazolam group. Remimazolam group was more sedated at the time of admission to PACU. Pain intensity and the requirement for analgesics were lower in the remimazolam group than in the propofol group.
Conclusions: Remimazolam-based total intravenous anesthesia provided a similar QoR to propofol. Remimazolam and propofol can be used interchangeably for general anesthesia in female patients undergoing thyroid surgery.

1. Introduction

Remimazolam is a newly developed ultra-short-acting benzodiazepine with advantages such as rapid onset and offset, a high safety profile in terms of hemodynamic stability, and reversal agent availability [1]. Multiple randomized clinical trials have demonstrated its safety and efficacy as a sedative and general anesthetic, compared with midazolam or propofol [2–4]. However, little is known about its impact on prognosis in terms of overall recovery after anesthesia and surgery, which is becoming an increasingly important aspect for determining the utility of an anesthetic agent.

Considering the remarkable advances in surgical techniques,

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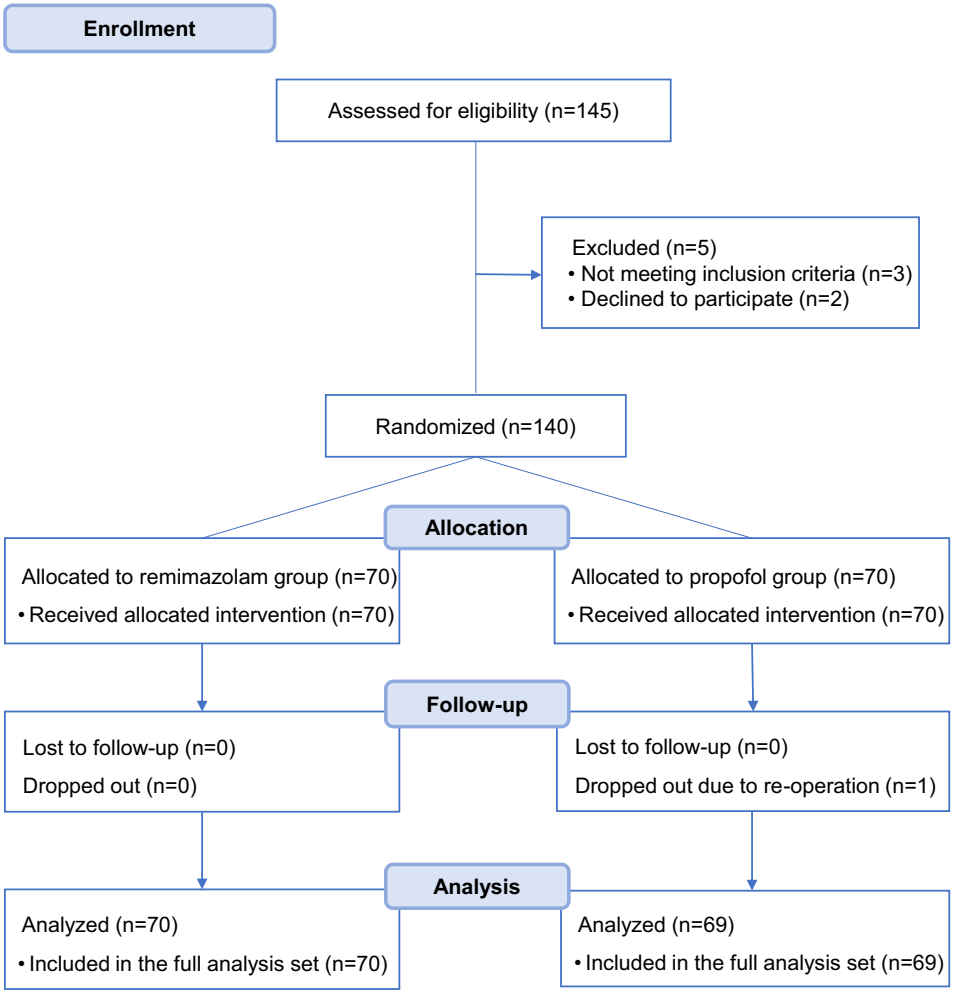

Fig. 1. CONSORT diagram describing patient progress through each stage of the randomized trial.

sedation, and pain management, current perioperative care for improving the recovery of surgical patients focuses on the patients' subjective postoperative experience rather than morbidity endpoints alone [5]. The quality of recovery (QoR) score is an objective measure of patient-centered general health status after surgery and anesthesia [6]. Its latest version, QoR-15, is characterized by time-efficiency and a high rate of response and completion [7], and it has been validated in patients undergoing various surgical procedures [8].

In various surgical cohorts over the last decade, propofol-based total intravenous anesthesia (TIVA) has been shown to be associated with better QoR than balanced inhalational anesthesia [9,10]. The possible reason was stated to be the ability of propofol to modulate perioperative stress, inflammatory response, and physiologic deterioration [9,10]. Nevertheless, propofol-based general anesthesia has certain drawbacks, including injection pain, cardiorespiratory depression, and the risk of a rare but fatal metabolic derangement [1,11]. If the benefit of propofol-based TIVA in terms of QoR could be achieved by another anesthetic without the aforementioned side effects, it would increase the available choices of anesthetic methods. In this study, we aimed to compare QoR assessed by QoR-15 scores between remimazolam-based TIVA and propofol-based TIVA. Our primary hypothesis was that the QoR-15 on postoperative day 1 (POD1) in females receiving thyroidectomy under remimazolam-based TIVA would be non-inferior to that in patients receiving propofol-based TIVA.

2. Methods

2.1. Ethics and recruitment

This prospective, double-blind, randomized trial was approved by the Institutional Review Board of Yonsei University Health System Gangnam Severance Hospital (IRB #3–2021-0303) and was registered at ClinicalTrials.gov (NCT05016518). After obtaining written informed consent, female patients aged 20–65 years with American Society of Anesthesiologists (ASA) physical status I–III who were scheduled for open thyroidectomy between September 2021 and May 2022 were included. Patients with a known history of allergy to any study drug, current sedative opioid, or sleep aid medication, psychiatric or neurological disorders, BMI > 30 kg/m^2, and pregnancy were excluded.

2.2. Design

Patients were randomly assigned to the remimazolam and propofol groups in a 1:1 ratio using a computer-generated random sequence and sealed envelope method by a medical statistician (HS Lee, Ph.D). Patients, operators, and study investigators were blinded to group identity, while the attending anesthesiologist could not be blinded to group identity because of the significantly different properties of the two anesthetics. The remimazolam group received continuous remimazolam infusions at a rate of 6 mg kg^{-1} h^{-1} for induction and 1–2 mg kg^{-1} h^{-1} for maintenance. The propofol group received an effect-site target-controlled infusion (TCI) of propofol with an effect-site concentration

Table 1
Demographic characteristics and intraoperative data.

	Remimazolam ($N = 70$)	Propofol ($N = 69$)	Absolute standardized difference	p-value
Age (y)	39.5 [33–48]	41.0 [37–47]	0.1	0.350
Height (cm)	159.3 ± 18.0	161.4 ± 4.6	0.2	0.337
Weight (kg)	58.2 ± 8.4	60.4 ± 7.3	0.3	0.105
ASA physical status, n (%)				0.959
I	51 (72.9)	50 (72.5)	0.0	
II	19 (27.1)	19 (27.5)	0.0	
Surgical type, n (%)				0.496
Partial thyroidectomy	1 (1.4)	1 (1.5)	0.0	
Total thyroidectomy	67 (95.7)	63 (91.3)	0.2	
Thyroidectomy combined with RND	2 (2.9)	5 (7.3)	0.2	
Duration of anesthesia (min)	52.7 ± 22.8	58.8 ± 22.0	0.3	0.114
Total amount of anesthetic drug (mg)				–
Remimazolam	84.0 [65–103]	–		
Propofol	–	576.0 [433–680]		
Injection pain, n (%)	0 (0)	2 (2.9)	0.1	0.245
Total amount of remifentanil (mcg)	458.0 [319–576]	452.0 [336–533]	0.0	0.998
Need of inotropes or vasopressors, n (%)	4 (5.7)	9 (13.0)	0.3	0.138
Total amount of ephedrine (mg)	0.0 [0–0]	0.0 [0–0]	0.0	0.092
Total amount of phenylephrine (mcg)	0.0 [0–0]	0.0 [0–0]	0.0	0.488

Data are presented as the mean ± SD, median [interquartile range], or number of patients (%).
ASA: American Society of Anesthesiologists; RND: radical neck dissection.

(Ce) of 5 μg mL^{-1} and 2–6 μg mL^{-1} for anesthesia induction and maintenance, respectively.

All patients underwent standardized surgical and anesthetic care, except for the type of general anesthetic agent used. There was no premedication given prior to anesthesia. Routine monitoring was initiated upon arrival in the operating room, including an electrocardiogram, pulse oximetry, non-invasive blood pressure, acceleromyography (TOF-watch SX; MSD, Haarlem, the Netherlands), and patient state index (PSI, SedLine®, Masimo Corp., CA, USA). All patients received 0.1 mg of glycopyrrolate followed by an effect-site TCI of remifentanil with 2 ng mL^{-1} Ce. The induction dose of remimazolam (6 mg kg^{-1} h^{-1}) or propofol (5 μg mL^{-1} Ce) was administered according to the group allocation, followed by the administration of 0.6 mg kg^{-1} of rocuronium and 4 ng mL^{-1} Ce of remifentanil after confirmation of loss of consciousness (LOC), defined as loss of verbal response and eyelash reflex. At a PSI < 50 and train-of-four count = 0, the patient's trachea was intubated with a 7.0 mm (internal diameter) tracheal tube using a video laryngoscope (McGRATH™ MAC Video Laryngoscope; Medtronic, Minneapolis, MN, USA). The anesthetic administration rate was adjusted to the study protocol's maintenance dose (1–2 mg kg^{-1} h^{-1} for remimazolam and 2–6 μg mL^{-1} Ce for propofol) and 2–6 ng mL^{-1} Ce of remifentanil, aiming to maintain a PSI range between 25 and 50 and mean arterial pressure (MAP) within 20% of preoperative baseline values. TCI was performed on the basis of pharmacokinetic models developed by Minto [12] and Schnider [13] for remifentanil and propofol, respectively, using a commercial TCI pump (Orchestra Base Primea; Fresenius Vial, Brezins, France). Normal saline (NS) was used as a main fluid during surgery in all patients to avoid precipitate formation with the lactate solution and remimazolam.

Mechanical ventilation was maintained with a tidal volume of 6–8 mL kg^{-1} predicted body weight and a positive end-expiratory pressure of 5 cm H_2O. The respiratory rate was adjusted to maintain an end-tidal carbon dioxide concentration of 30–35 mmHg with an air/oxygen mixture (fraction of inspired oxygen, 0.5). The oropharyngeal temperature was kept between 36 and 37 °C. NS 100 mL, ephedrine 4 mg, or phenylephrine 30 μg were administered as appropriate when the MAP was decreased to <65 mmHg or 20% of the baseline value under adequate depth of anesthesia. All patients received 1 g of acetaminophen and 0.3 mg of ramosetron 30 min before the end of surgery for postoperative analgesia and anti-emetic prophylaxis, respectively. At the end of surgery, all anesthetics were discontinued, and 1 mg of neostigmine with 0.2 mg of glycopyrrolate was administered at a train-of-four ratio of >90% to reverse residual neuromuscular block. Tracheal extubation was performed after confirming the recovery of consciousness (ROC), defined as responses to verbal commands and sufficient spontaneous breathing, and patients were transferred to the post-anesthesia care unit (PACU).

In the PACU, fentanyl 1 μg kg^{-1} and metoclopramide 10 mg were administered to relieve pain and nausea/vomiting, respectively, if the numerical rating scale (NRS, ranging from 0 to 10) exceeded 3. The patients were discharged to the ward at a Richmond Agitation Sedation Scale (RASS) score of 0. In the ward, ketolorac 50 mg and ramosetron 0.3 mg were administered twice daily as analgesics and anti-emetic drugs, respectively. Tramadol (50 mg) and metoclopramide (10 mg) were given if the NRS score exceeded 4. Patients were discharged from the hospital according to the type of surgery and the discretion of the surgeons, who were blinded to the group allocation.

2.3. Outcome measures

The main goal of this study was to assess the QoR using the QoR-15 questionnaire, which is a global measure of recovery after surgery that evaluates five dimensions of recovery: physical comfort (5 items), physical independence (2 items), emotional state (4 items), psychological support (2 items), and pain (2 items). Each item is rated on an 11-point scale based on its frequency on the questionnaire (greater score at greater frequency for positive items and less frequency for negative items). The total score ranged from 0 (poorest recovery quality) to 150 (best recovery quality). The patients completed the QoR-15 questionnaire at three time points: the day before surgery; POD1; and POD2 (between 4 pm and 6 pm). The POD1 score was the primary outcome of interest.

Additional assessments included the following: total amount of anesthetic drugs and remifentanil administered during surgery; hemodynamic data including MAP, heart rate (HR), and SpO_2 before induction, immediately after tracheal intubation, at cessation of anesthetics, immediately after extubation, at arrival and discharge from PACU; PSI values before induction, immediately after tracheal intubation, at cessation of anesthetics, immediately after extubation; required amounts of anesthetics for LOC; time to LOC; time to ROC; time to extubation; RASS upon PACU arrival; profiles of pain and postoperative nausea and vomiting (PONV) at the PACU and ward including maximal NRS pain score; incidence of nausea/vomiting; administration of rescue analgesic and anti-emetic agents; duration of PACU stay; length of hospital stay after surgery; and complications including wound infection, hematoma, recurrent laryngeal nerve injury, and thyroid storm.

2.4. Statistical analysis

Considering that propofol-based TIVA has resulted in an excellent QoR in various types of surgeries, including thyroidectomy [9,14], we decided to perform a non-inferiority study to compare the impact of

Table 2
Global and 5 dimensional QoR-15 scores between the remimazolam and propofol groups preoperatively and on postoperative days 1 and 2.

	Remimazolam (N = 70) mean ± SD	Propofol (N = 69)mean ± SD	Mean difference (95% CI)	p-value	Bonferroni corrected p-value
Global QoR-15					0.349[a]
Preop	134.0 ± 8.4	132.0 ± 10.0	2.0 (−1.1, 5.1)	0.205	0.616
POD1	111.2 ± 18.8	109.1 ± 18.9	2.1 (−4.2, 8.5)	0.504	>0.999
POD2	124.8 ± 14.9	123.7 ± 16.5	1.1 (−4.1, 6.4)	0.668	>0.999
Emotional status					0.338[a]
Preop	30.4 ± 5.1	30.2 ± 6.1	0.2 (−1.7, 2.1)	0.825	>0.999
POD1	32.0 ± 6.3	30.8 ± 7.2	1.2 (−1.0, 3.5)	0.288	0.864
POD2	34.3 ± 5.6	33.6 ± 5.3	0.7 (−1.1, 2.5)	0.436	>0.999
Physical comfort					0.639[a]
Preop	44.4 ± 4.6	43.0 ± 4.6	1.4 (−0.2, 2.9)	0.077	0.232
POD1	36.6 ± 8.4	37.0 ± 8.2	−0.4 (−3.2, 2.4)	0.793	>0.999
POD2	42.2 ± 4.9	42.2 ± 6.3	0.0 (−1.8, 1.9)	0.966	>0.999
Psychological support					0.711[a]
Preop	19.4 ± 1.2	19.4 ± 1.0	0.0 (−0.4, 0.3)	0.912	>0.999
POD1	16.0 ± 2.7	15.9 ± 2.9	0.1 (−0.9, 1.0)	0.878	>0.999
POD2	17.1 ± 2.2	16.8 ± 2.8	0.3 (−0.6, 1.1)	0.545	>0.999
Physical independence					0.382[a]
Preop	19.8 ± 0.7	19.7 ± 0.6	0.1 (−0.1, 0.3)	0.502	>0.999
POD1	14.5 ± 3.1	14.0 ± 3.7	0.5 (−0.7, 1.6)	0.405	>0.999
POD2	16.4 ± 2.2	16.1 ± 2.9	0.2 (−0.6, 1.1)	0.581	>0.999
Pain					0.271[a]
Preop	20.0 ± 0.0	19.8 ± 1.1	0.2 (−0.0, 0.5)	0.077	0.231
POD1	12.1 ± 3.6	11.2 ± 3.7	1.0 (−0.3, 2.2)	0.124	0.372
POD2	14.9 ± 3.3	15.0 ± 3.7	−0.1 (−1.3, 1.0)	0.805	>0.999

Data are presented as the mean ± SD.
QoR-15: Quality of Recovery-15; CI: confidence interval; POD1: postoperative day 1; POD2: postoperative day 2.
[a] p-value of the group and time interaction obtained by the linear mixed model.

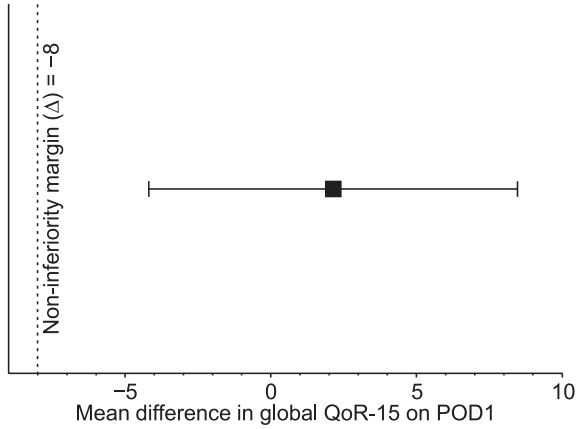

Fig. 2. Mean difference in global QoR-15 on POD1. The data are plotted as mean ± 95% CI. Vertical line at −8 represents margin of non-inferiority for the global QoR-15. QoR-15: Quality of Recovery-15; POD1: postoperative day 1; CI: confidence interval.

remimazolam on the primary study endpoint (QoR-15) to that of propofol. Based on previous studies that defined the minimal clinically important difference (MCID) of QoR-15 as 8 [8,15], the non-inferiority margin for the difference in means between the groups in the current study was set at −8. We declared non-inferiority of remimazolam-based TIVA relative to propofol-based TIVA if the lower limit of the 95% confidence interval (CI) of the difference in QoR-15 was above −8. According to our preliminary data, the sample size calculation for the non-inferiority test based on the primary endpoint indicated that 124 patients (62 per group) were sufficient to show non-inferiority with a margin of −8 and a 2.5% one-sided significance level, assuming an standard deviation (SD) of 16 according to our preliminary data. We determined a sample size of 70 participants in each group, considering a 10% dropout rate.

Continuous data are presented as the mean (SD) or median (interquartile range) with comparisons made using Student's t-test or the Wilcoxon rank-sum test, as appropriate, according to normality distribution. Categorical data are presented as a percentage of the total number of patients with comparisons made using the chi-square test or Fisher's exact test, as appropriate. Standardized differences were used to compare the balance in the demographic and operative data between groups [16]. The P-value from the Bonferroni method was also calculated for the primary end point (QoR-15) to adjust for increases in type I error due to multiple tests. The QoR-15 and hemodynamic variables were analyzed using a linear mixed model with unstructured covariance matrix clustering on record identification as a random effect and group, time, and group-by-time as fixed effects. When there was a significant interaction among group, time, and group-by-time variables, post-hoc analysis with Bonferroni correction was performed to adjust for multiple comparisons. Analysis was performed for the full analysis sets, which included all randomized participants who did not fail to respond to QoR-15 questionnaires postoperatively, regardless of the group they were allocated to. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$.

3. Results

Among the 145 patients who were assessed for eligibility, 140 subjects who provided consent were enrolled and randomly assigned to either the remimazolam or propofol groups. One patient in the propofol group was excluded after inclusion because of an emergent reoperation for postoperative bleeding (dropout). Therefore, we analyzed data from 139 patients, 70 and 69 of whom were included in the remimazolam and propofol groups, respectively (Fig. 1). The baseline characteristics and intraoperative data are depicted in Table 1. The patient characteristics were well balanced between the two groups. The total amounts of remimazolam and propofol administered during the surgery were 84.0 [65–103] mg and 576.0 [433–680] mg, respectively. The total amount of remifentanil used and the need for inotropes or vasopressors did not differ between groups.

The QoR-15 scores are presented in Table 2. The global QoR-15 score on POD1 in the remimazolam group was non-inferior to that in the propofol group (111.2 [18.8] vs. 109.1 [18.9]), with a mean difference of 2.1 [95% CI −4.2, 8.5]; the lower limit was greater than the non-

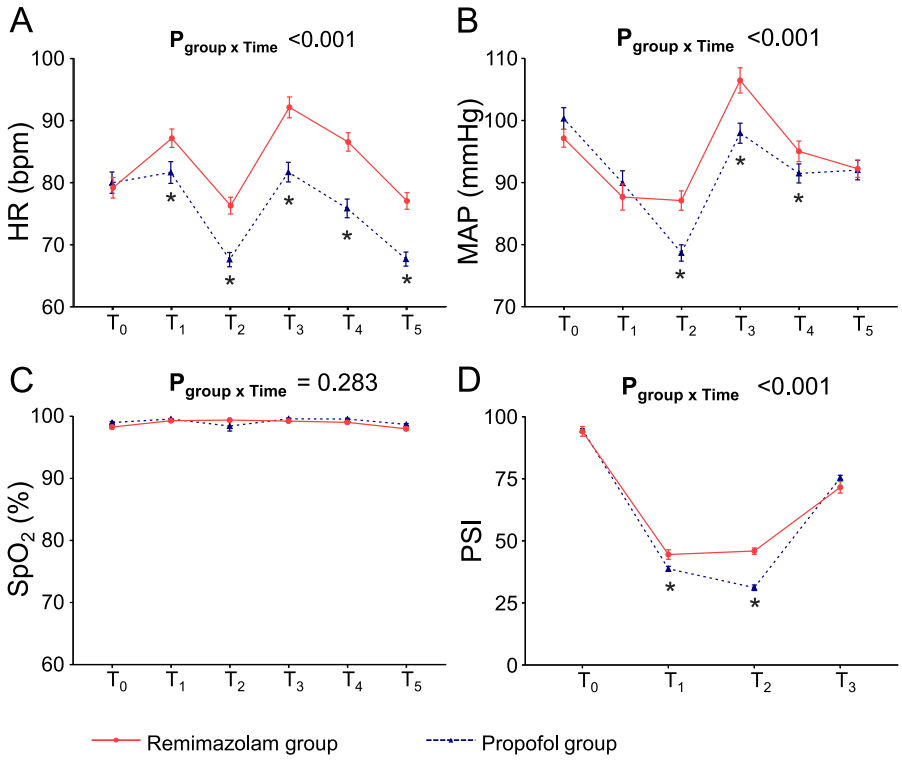

Fig. 3. Perioperative hemodynamic variables including (A) HR, (B) MAP, (C) SpO_2, (D) PSI. Values represent the estimated means from linear mixed models with standard error. T_0: before induction; T_1: immediately after intubation; T_2: at cessation of anesthetics; T_3: immediately after extubation; T_4: at PACU arrival; T_5: at discharge from PACU; Pgroup x Time: *p*-value of the group and time interaction obtained by the linear mixed model. *$P < 0.05$ in post-hoc analysis. HR: heart rate; MAP: mean arterial pressure; SpO_2: pulse oxygen saturation; PSI: patient state index; post-anesthesia care unit: PACU.

inferiority margin of −8 ($p = 0.002$ for non-inferiority; Fig. 2). None of the five dimensions differed between the groups. The POD2 scores were comparable between the groups. In the linear mixed model analysis, the global and dimensional QoR-15 scores on POD1 were significantly decreased compared with the preoperative scores in both groups ($P <$ 0.001 for each), while the changes over time were not significantly different between the groups.

The perioperative hemodynamic variables are shown in Fig. 3 and Supplemental Table 1. Changes in HR, MAP, and PSI over time were significantly different between the groups ($P < 0.001$ for each). Post-hoc analysis showed that the HR was significantly higher in the remimazolam group than in the propofol group at all time points after induction. MAP was significantly higher in the remimazolam group at the cessation of anesthesia ($P < 0.001$), immediately after extubation ($P < 0.001$), and at PACU arrival ($P = 0.007$). PSI values were significantly higher in the remimazolam group than in the propofol group after tracheal intubation ($P = 0.001$) and at the cessation of anesthetics ($P < 0.001$). There was no significant difference in SpO_2 change over time between the two groups. A comparison of hypotensive events between the groups is shown in Supplemental Table 2. The proportion of patients who showed MAP <65 mmHg at cessation of anesthetics was higher in the propofol group than in the remimazolam group (10.1% vs. 1.4%, $P = 0.033$). More patients in the propofol group exhibited MAP <20% below baseline value compared with those in the remimazolam group after cessation of anesthetics (55.1% vs. 25.7%, $P < 0.001$) and at PACU arrival (17.4% vs. 5.7%, $P = 0.031$).

Table 3 shows LOC and ROC profiles as well as postoperative data. The time from administration of remimazolam to LOC was 115 s, which was significantly longer than that in the propofol group (70 s; $P <$ 0.001). The time of ROC, time of self-respiration recovery, and time for extubation were similar in both groups. The RASS score at PACU admission was significantly lower in the remimazolam group than in the propofol group (−2.0 [−3−−2] vs. −2.0 [−2−−1], $P = 0.005$). None of the patients exhibited agitated behavior. The maximal NRS pain score, the number of patients requiring rescue analgesics, and the amount of fentanyl administered during the PACU stay were all significantly lower in the remimazolam group than in the propofol group (3.0 [2–4] vs 4.0 [3–7], $P < 0.001$; 17 (24.3%) vs. 33 (47.8%), $P = 0.004$; and 0 [0–0] μg vs 0 [0–50] μg, $P = 0.001$, respectively). Three patients in the remimazolam group complained of nausea, while in the propofol group, none of the patients experienced nausea. However, this difference was not statistically significant. The length of PACU stay did not differ between the groups. In the ward, there were no significant differences in terms of pain or PONV. The postoperative complications and length of hospital stay were similar between the groups.

4. Discussion

Remimazolam, despite being a new drug, is becoming rapidly established in clinical practice due to its utility as a sedative-anesthetic agent based on its rapid on/offset without considerable side effects [17–19]. Comparing remimazolam with propofol seems inevitable, as the latter has dominated the field of TIVA and procedural sedation till date. Some of the previous comparisons for safety and efficacy of remimazolam revealed similar or even superior properties, raising hopes for its active use as a propofol substitute [3,4]. Currently, subjective well-being and satisfaction of surgical patients are prioritized. Thus, the benefit to QoR would be a milestone that would enable the use of remimazolam as the main anesthetic agent. Considering that propofol-based TIVA has consistently shown a greater performance on the postoperative QoR than modern inhaled anesthetics [9,14], we conducted a non-inferiority test for the comparison and demonstrated the non-inferiority of remimazolam to propofol with respect to QoR-15 score on POD1 in female patients undergoing thyroidectomy. The non-inferiority was also preserved when the margin was set as −6 according to the recent update on the MCID of the QoR-15 [20]. The remimazolam-based TIVA did not show any significant differences from the propofol-based TIVA in all five dimensions of QoR. This result suggests that remimazolam fulfills one of the prerequisites for general anesthesia, at least in female patients undergoing minor surgery.

In a previous pioneering clinical trial that reported the benefit of propofol-based TIVA compared with desflurane anesthesia [14],

Table 3
Profiles of LOC and ROC and postoperative outcomes.

	Remimazolam (N = 70)	Propofol (N = 69)	Mean difference (95% CI)	p-value
Time to LOC (*sec*)	115.0 [89–126.5]	70.0 [60–85]	35.5 (20, 51)	<0.001
Dose for LOC (mg)				–
Remimazolam	11.9 [10.2–14.6]	–		
Propofol	–	96.0 [89–108]		
Time to ROC (min)	10.0 [8–13]	10.0 [8–13]	0.0 (−1,1)	0.931
Time to recovery of self-respiration (min)	9.0 [8–13]	10.0 [8–13]	0.0 (−1, 1)	0.769
Time to extubation (min)	10.5 [8–14]	11.0 [9–13]	0.0 (−1, 1)	0.985
PACU data				
RASS at admission (−5 ~ +4)	−2.0 [−3−−2]	−2.0 [−2−−1]	−0.5 (−1,0)	0.005
Maximal NRS pain score (0–10)	3.0 [2–4]	4.0 [3–7]	−1.0 (−2,0)	<0.001
Need of rescue analgesics, n (%)	17 (24.3)	33 (47.8)	−23.5 (−39.0, −8.1)	0.004
Fentanyl administered (mcg)	0.0 [0–0]	0.0 [0–50]	0.0 (0,0)	0.001
Nausea, n (%)	3 (4.3)	0 (0)	4.3 (−0.5, 9.0)	0.245
Vomiting, n (%)	0 (0)	0 (0)		>0.999
Need for rescue anti-emetics, n (%)	1 (1.4)	0 (0)	1.4 (−1.4, 4.2)	>0.999
Metoclopramide administered (mg)	0.0 [0–0]	0.0 [0–0]	0.0 (0, 0)	0.328
Duration of PACU stay (min)	40.0 [34–49]	40.0 [30–51]	0.0 (−3,3)	0.949
GW data				
Maximal NRS pain score (0–10)	4.0 [3–5]	4.0 [3–5]	0.0 (0, 0)	0.879
Need of rescue analgesics, n (%)	7 (10)	4 (5.8)	4.2 (−4.7, 13.1)	0.745
Tramadol administered (mg)	0.0 [0–0]	0.0 [0–0]	0.0 (0, 0)	0.574
Nausea, n (%)	1 (1.4)	2 (2.9)	−1.5 (−6.3, 3.4)	0.620
Vomiting, n (%)	0 (0)	1 (1.5)	−1.4 (−4.3, 1.4)	0.496
Need of rescue anti-emetics, n (%)	1 (1.4)	2 (2.9)	−1.5 (−6.3, 3.4)	0.620
Postoperative complications*, n (%)	1 (1.4)	1 (1.5)	0.0 (−4.0, 3.9)	>0.999
Duration of postoperative hospital stay (day)	2.0 [1–2]	2.0 [1–2]	0.0 (0, 0)	0.889

Data are presented as the median [interquartile range] or number of patients (%).

LOC: loss of consciousness; ROC: recovery of consciousness; CI: confidence interval; PACU: post-anesthesia care unit; RASS: Richmond Agitation and Sedation Scale; NRS: numerical rating scale; GW: general ward.

* Postoperative complications include wound infection, hematoma, recurrent laryngeal nerve injury, and thyroid storm.

physical comfort and physical independence, out of five dimensions of the QoR-40 questionnaires, substantially derived benefits from TIVA. The authors presumed that the underlying mechanism was related to its anti-emetic properties, modulatory effects on perioperative stress and inflammatory response, and scavenging of free radicals, which are now well recognized in academia. Remimazolam anesthesia was also found to be more effective than desflurane anesthesia in preventing PONV after laparoscopic gynecological surgery [21]. Given that the presence and severity of emesis have a significant impact on recovery, a similar incidence of PONV between our study groups would have contributed to the comparable QoR scores. In terms of anti-inflammatory properties, there are no comparative investigations between remimazolam and other hypnotics, including propofol. However, the potency of remimazolam to suppress systemic inflammatory responses has been reported recently. In a mouse model of endotoxemia, remimazolam administration decreased the release of pro-inflammatory cytokines with the inhibition of mitogen-activated protein kinase signaling and toll-like receptor 4-mediated inflammatory cascades [22]. Remimazolam has also been shown to have anti-inflammatory properties in animal models of cerebral ischemia-reperfusion injury [23] and sepsis-associated acute liver injury [24]. Further research is needed to determine if comparable impacts on the systemic inflammation and stress response after surgery could have contributed to the similar QoR scores.

Interestingly, the current results contradict the findings from a recent RCT by Mao et al., which revealed the superiority of propofol-based TIVA to remimazolam-based TIVA in postoperative QoR-15 [25]. In their study, physical comfort and emotional state were different between the groups. They attributed this to the re-emergence of discomfort, such as anxiety, following remimazolam anesthesia, which may have resulted from an undesirable desensitization-like effect at the top end of the response curve and a rebound phenomenon upon the termination of the agent [26]. If that explanation is true, we can speculate that this was not the case in our study because the total amount of remimazolam administered would not have reached the levels that may have caused the issues reported in the study by Mao et al., considering that the duration of anesthesia in our study was shorter than that in their study. Differences in demographics and surgical types could have also led to different results. The discordance in the results could be attributed to the study populations' differing gender composition; we enrolled female patients only, whereas Mao et al. studied both male and female patients, with the male patients constituting approximately 70% of the study population. A gender difference in the QoR after surgery has previously been demonstrated, which has been attributed primarily to the interaction of anesthetic drugs with sex hormones [27]. However, how different genders respond to the multifaceted properties of remimazolam, including its so-called rebound phenomenon, remains unknown and warrants further investigation.

Notably, pain intensity and analgesic consumption were significantly lower in the remimazolam group than in the propofol group in the immediate postoperative period. This could be linked to the deeper sedative states in the remimazolam group upon PACU arrival, as observed in the current study. However, the duration of PACU stay was similar between the groups and the difference in the RASS score was not clinically meaningful in terms of safety issues, such as hypoxia. Another reason for the better analgesic profile in the PACU might be the analgesic potency of remimazolam. In a mouse tail-flick pain model, remimazolam inhalation increased the analgesic effect of opioids [28]. A recent study demonstrated that neuropathic pain induced by spinal nerve ligation in rats was attenuated by the administration of remimazolam through the regulation of bradykinin receptor B1 and autophagy [29]. Despite this experimental evidence, remimazolam cannot be predicated as having better analgesic properties than propofol, which has been widely reported to possess analgesic and antihyperalgesic effects as well [30]. Moreover, the improved pain profile did not persist after PACU discharge, and the pain dimension of the QoR-15 did not show any difference between the groups. More sophisticated studies are needed to compare the analgesic and opioid-sparing effects between the two anesthetic methods in this regard. Consistent with previous reports [3,4,25], the remimazolam group showed considerably better preservation of blood pressure during surgery than the propofol group, which can be attributed to a difference in the suppressive effect on the cardiovascular system [31,32]. Nevertheless, we should not presume that remimazolam-based TIVA is completely safe for hemodynamic stability in relatively young healthy women, because there was a significant increase in HR upon intubation and extubation as well as a significant increase in MAP upon extubation compared to the baseline, which may

indicate insufficient attenuation of sympathetic activity by remimazolam.

There is a limitation to this study that should be noted. We are not convinced that the depth of anesthesia in the remimazolam group was optimal throughout the surgery because the accuracy of commercial processed electroencephalography, including the PSI, has not yet been determined [33]. Despite similar recovery times, our data showed that the remimazolam group had significantly higher PSI values than the propofol group. Nevertheless, the protocol is expected to be effective and safe, given our findings in terms of reasonable recovery time, absence of recall issues and abnormal agitative behaviors postoperatively.

Overall, we found that the QoR after remimazolam-based TIVA was non-inferior to that after propofol-based TIVA in female patients undergoing thyroidectomy. Hence, the former can be considered as an anesthetic method of choice for achieving a good QoR, comparable to that experienced by the patients subjected to propofol-based TIVA.

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Author statement

All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2022.110955.

References

[1] Sneyd JR, Gambus PL, Rigby-Jones AE. Current status of perioperative hypnotics, role of benzodiazepines, and the case for remimazolam: a narrative review. Br J Anaesth 2021;127:41–55.
[2] Zhu X, Wang H, Yuan S, Li Y, Jia Y, Zhang Z, et al. Efficacy and safety of remimazolam in endoscopic sedation-a systematic review and Meta-analysis. Front Med (Lausanne) 2021;8:655042.
[3] Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. J Anesth 2020;34:543–53.
[4] Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA class III): results of a multicenter, randomized, double-blind, parallel-group comparative trial. J Anesth 2020;34:491–501.
[5] Wessels E, Perrie H, Scribante J, Jooma Z. Quality of recovery in the perioperative setting: a narrative review. J Clin Anesth 2022;78:110685.
[6] Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth 2000;84:11–5.
[7] Yoon S, Joo H, Oh YM, Lee J, Bahk JH, Lee HJ. Validation and clinical utility of the Korean version of the quality of Recovery-15 with enhanced recovery after surgery: a prospective observational cohort study. Br J Anaesth 2020;125:614–21.
[8] Kleif J, Waage J, Christensen KB, Gögenur I. Systematic review of the QoR-15 score, a patient- reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth 2018;120:28–36.
[9] Shui M, Xue Z, Miao X, Wei C, Wu A. Intravenous versus inhalational maintenance of anesthesia for quality of recovery in adult patients undergoing non-cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. PLoS One 2021;16:e0254271.
[10] Joe YE, Kang CM, Lee HM, Kim KJ, Hwang HK, Lee JR. Quality of recovery of patients who underwent curative pancreatectomy: comparison of Total intravenous anesthesia versus inhalation anesthesia using the QOR-40 questionnaire. World J Surg 2021;45:2581–90.
[11] Liolios A, Guerit JM, Scholtes JL, Raftopoulos C, Hantson P. Propofol infusion syndrome associated with short-term large-dose infusion during surgical anesthesia in an adult. Anesth Analg 2005;100:1804–6.
[12] Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJM, Gambus PL, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil 1. Model development. Anesthesiology. 1997;86:10–23.
[13] Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, et al. The influence of age on propofol pharmacodynamics. Anesthesiology. 1999;90:1502–16.
[14] Lee WK, Kim MS, Kang SW, Kim S, Lee JR. Type of anaesthesia and patient quality of recovery: a randomized trial comparing propofol-remifentanil total i.v. anaesthesia with desflurane anaesthesia. Br J Anaesth 2015;114:663–8.
[15] Myles PS, Myles DB, Galagher W, Chew C, MacDonald N, Dennis A. Minimal clinically important difference for three quality of recovery scales. Anesthesiology. 2016;125:39–45.
[16] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107.
[17] Rex DK, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etzkorn K, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. Gastrointest Endosc 2018;88:427–37. e6.
[18] Borkett KM, Riff DS, Schwartz HI, Winkle PJ, Pambianco DJ, Lees JP, et al. A phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. Anesth Analg 2015;120:771–80.
[19] Pastis NJ, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, et al. Safety and efficacy of Remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest. 2019;155:137–46.
[20] Myles PS, Myles DB. An updated minimal clinically important difference for the QoR-15 scale. Anesthesiology. 2021;135:934–5.
[21] Hari Y, Satomi S, Murakami C, Narasaki S, Morio A, Kato T, et al. Remimazolam decreased the incidence of early postoperative nausea and vomiting compared to desflurane after laparoscopic gynecological surgery. J Anesth 2022;36:265–9.
[22] Liu X, Lin S, Zhong Y, Shen J, Zhang X, Luo S, et al. Remimazolam protects against LPS-induced endotoxicity improving survival of endotoxemia mice. Front Pharmacol 2021;12:739603.
[23] Shi M, Chen J, Liu T, Dai W, Zhou Z, Chen L, et al. Protective effects of remimazolam on cerebral ischemia/reperfusion injury in rats by inhibiting of NLRP3 Inflammasome-dependent pyroptosis. Drug Des Devel Ther 2022;16:413–23.
[24] Fang H, Zhang Y, Wang J, Li L, An S, Huang Q, et al. Remimazolam reduces sepsis-associated acute liver injury by activation of peripheral benzodiazepine receptors and p38 inhibition of macrophages. Int Immunopharmacol 2021;101:108331.
[25] Mao Y, Guo J, Yuan J, Zhao E, Yang J. Quality of recovery after general anesthesia with Remimazolam in Patients' undergoing urologic surgery: a randomized controlled trial comparing Remimazolam with Propofol. Drug Des Devel Ther 2022;16:1199–209.
[26] Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: pharmacologic considerations and clinical role in anesthesiology. Pharmacotherapy. 2016;36:1021–7.
[27] Buchanan FF, Myles PS, Cicuttini F. Effect of patient sex on general anaesthesia and recovery. Br J Anaesth 2011;106:832–9.
[28] Bevans T, Deering-Rice C, Stockmann C, Rower J, Sakata D, Reilly C. Inhaled Remimazolam potentiates inhaled remifentanil in rodents. Anesth Analg 2017;124:1484–90.
[29] Xie H, Lu F, Liu W, Wang E, Wang L, Zhong M. Remimazolam alleviates neuropathic pain via regulating bradykinin receptor B1 and autophagy. J Pharm Pharmacol 2021;73:1643–51.
[30] Bandschapp O, Filitz J, Ihmsen H, Berset A, Urwyler A, Koppert W, et al. Analgesic and antihyperalgesic properties of propofol in a human pain model. Anesthesiology. 2010;113:421–8.
[31] de Wit F, van Vliet AL, de Wilde RB, Jansen JR, Vuyk J, Aarts LP, et al. The effect of propofol on haemodynamics: cardiac output, venous return, mean systemic filling pressure, and vascular resistances. Br J Anaesth 2016;116:784–9.
[32] Soleimani A, Heidari N, Habibi MR, Kiabi FH, Khademloo M, Emami Zeydi A, et al. Comparing hemodynamic responses to diazepam, Propofol and etomidate during anesthesia induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft surgery: a double-blind. Randomized Clinical Trial Med Arch 2017;71:198–203.
[33] Shirozu K, Nobukuni K, Tsumura S, Imura K, Nakashima K, Takamori S, et al. Neurological sedative indicators during general anesthesia with remimazolam. J Anesth 2022;36:194–200.