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CLINICAL TRIAL REPORT

Comparing Remimazolam and Propofol for Postoperative Anesthesia Satisfaction in Outpatient Gynecological Surgery: A Randomized Clinical Trial

Xu-Lin Wang[1,*], Ling-Ling Dai[2,*], Yan-Na Li[1], Jian-Wen Zhang[1], Ming-Cui Qu[1], Yao-Yao Zhou[1], Na Xing[1]

[1]Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China; [2]Department of Respiration, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Na Xing, Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Zhengzhou, People's Republic of China, Tel +8613949095172, Email 16427485@qq.com

Purpose: This study aimed to compare the efficacy of remimazolam and propofol regarding postoperative anesthesia satisfaction in patients undergoing outpatient gynecological surgery.

Patients and Methods: This was a single-center, open-label, non-inferiority, randomized clinical trial. Patients aged ≥ 18 years who underwent outpatient gynecological surgery with sedation were enrolled. Participants were randomly assigned to be sedated with remimazolam or propofol. The primary endpoint was the immediate postoperative anesthesia satisfaction score, evaluated through the Iowa Satisfaction with Anesthesia Scale (ISAS).

Results: 168 patients were randomly allocated to either the remimazolam group (n = 84) or the propofol group (n = 84). The mean (standard deviation) ISAS scores immediately after surgery were 1.7 (0.6) for the remimazolam group and 2.0 (0.7) for the propofol group (difference, –0.2; 97.5% confidence interval [CI]: –0.5 to –0.0; $p = 0.02$), indicating non-inferiority. The length of post-anesthesia care unit (PACU) stay was longer in the remimazolam group than in the propofol group (27.6 [9.1] min vs 22.4 [7.0] min; difference, 5.2 [95% CI: 2.7 to 7.6] min; $p < 0.001$). High-intensity injection pain was less frequently observed in the remimazolam group than in the propofol group (3.6% vs 45.2%; difference, –41.7% [95% CI: –54.2% to –29.1%]; $p < 0.001$). The nausea score was higher in the remimazolam group immediately after surgery than in the propofol group. Pain, nausea, sleep quality, anxiety, and depression scores were higher in the remimazolam group than in the propofol group on postoperative day 1. The incidence of adverse events and other secondary endpoints was comparable between the two groups.

Conclusion: Remimazolam was non-inferior to propofol regarding postoperative anesthesia satisfaction in patients undergoing outpatient gynecological surgery. Therefore, it should be considered as a new sedation alternative in such procedures.

Keywords: remimazolam, propofol, patient satisfaction, outpatient gynecological surgery, sedation

Introduction

Increasingly, there has been a noticeable trend towards performing minor gynecological surgeries in outpatient settings, driven by the goals of cost-effectiveness, patient convenience, faster recovery, and reduced risks of infections and respiratory complications.[1] Effective pain management in such surgery is crucial for ensuring both the safe and successful performance of procedures and patient comfort, which are the primary objectives of outpatient gynecological surgery.[2] Despite the availability of various analgesic modalities, including local anesthesia, oral or intravenous analgesics, sedation, and general anesthesia,[3–5] many patients still experience moderate to severe pain during these

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surgeries.[3,5] Research suggests that deep sedation might be a better choice for this population and associated with a reduced incidence of anesthesia-related complications.[4,6–8]

Currently, sedative drug options for outpatient gynecological surgery are scarce. Due to its rapid onset, short half-life, and swift recovery, propofol stands as the preferred sedative for outpatient procedures.[9,10] It is effectively used in conjunction with opioids for sedation in outpatient gynecological surgeries, including dilation and curettage, hysteroscopic examinations, and hysteroscopic surgeries.[6,11–13] However, its use raises significant concerns regarding adverse reactions, including hypotension, hypoxemia, and injection pain.[14,15] Moreover, midazolam, another commonly used sedative, carries a reduced risk of hypotension or respiratory depression compared to propofol. Nevertheless, its slow onset and prolonged half-life result in delayed emergence, which might not be ideal for short outpatient procedures.[16,17] Therefore, it is of utmost importance to investigate novel sedative agents to expand the options available to clinicians.

Remimazolam, a novel benzodiazepine, offers advantages of rapid onset, hemodynamic stability, and reversibility.[18] Research indicates that remimazolam is a safe and effective sedative or anesthetic agent for various procedures, including gastrointestinal endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), bronchoscopy, and hysteroscopy.[19–22] Additionally, remimazolam has been used to induce and maintain anesthesia in urological and thyroid surgeries.[23,24] Notably, studies show that patients undergoing gastrointestinal endoscopy and bronchoscopy with remimazolam sedation reported satisfaction scores comparable to or exceeding those of patients sedated with propofol.[25–28] However, data regarding the use of remimazolam in outpatient gynecological surgeries, particularly in terms of patient satisfaction, are limited.

Modern anesthesiology increasingly emphasizes patient-centered research endpoints, such as quality of life and satisfaction.[29] Therefore, this study used the Iowa Satisfaction with Anesthesia Scale (ISAS) to assess patient satisfaction with anesthesia, with the aim of evaluating the efficacy and safety of sedation with remimazolam in outpatient gynecological surgery. We hypothesized that remimazolam would be non-inferior to propofol concerning postoperative anesthesia satisfaction in outpatient gynecological surgery.

Materials and Methods

Study Design

This single-center, open-label, non-inferiority, randomized clinical trial was conducted at a tertiary care center in China (the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China) from October 2023 to March 2024. Pre-enrolment approval (2023-KY-0837-002) was obtained from the institutional review board. The study was registered in the Chinese Clinical Trial Registry (ChiCTR2300075545) and followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for trial reporting. Additionally, the study conformed to the Declaration of Helsinki, and all participants provided written informed consent.

Study Population

Patients aged ≥ 18 years who underwent outpatient gynecological surgery under sedation were eligible for inclusion. Patients were excluded from the study if they met any of the following criteria: BMI ≥ 30 kg/m²; difficult airway; known allergy to benzodiazepines, opioids, or propofol; alcohol dependence or drug addiction; severe dementia or language impairment; history of schizophrenia, Parkinson's disease, epilepsy, or myasthenia gravis; need for breastfeeding; history of delayed emergence from anesthesia; refusal to participate; participation in other clinical trials.

Randomization and Masking

A statistician not involved in patient recruitment used the R software to generate randomization sequences, allocating patients in a 1:1 ratio to either the remimazolam or propofol groups. The permuted block randomization method was used, with 4, 6, or 8 block sizes. Numbered and sealed opaque envelopes were then generated based on this randomization sequence and used by anesthesiologists for patient assignment. The anesthesiologists were unblinded to the group allocation due to the distinctive appearance of the two medications, while the patients, clinicians, and outcome assessors remained blinded.

Procedures

Preoperative fasting for 8 h for solids and 2 h for liquids is standard practice. Upon arrival in the operating room, peripheral venous access was established. Continuous monitoring of pulse oxygen saturation, electrocardiography, and heart rate was performed. Noninvasive blood pressure was automatically measured at three-minute intervals. Normal saline solution was continuously administered from the initiation of the surgery until the patient was discharged. Anesthesia machines and standard equipment in our gynecology outpatient surgical facility are readily available. Pre-oxygenation was performed before induction, followed by oxygen administration via face mask (6 L/min) throughout the sedation process. The depth of sedation was monitored during the procedure using the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S), with assessments conducted every minute by the anesthesiologist. Since anesthesiologists with expertise in airway management are the primary anesthesia practitioners in China, we opted to perform the procedure under deep sedation (MOAA/S < 2). To induce sedation in the patients, an initial bolus of remimazolam (0.2–0.3 mg/kg) or propofol (1.5–3 mg/kg) was administered, followed by a single intravenous dose of remifentanil (0.5–1 μg/kg). Top-up doses of remimazolam (2.5 mg) or propofol (0.5 mg/kg) were administered to sustain sedation. If inadequate analgesia is observed during surgery, remifentanil may be administered at 10–20 μg. A rescue medication of 50 mg propofol was administered if, within 15 min after administering the initial bolus dose, five top-up doses were administered without achieving the required sedation levels or meeting the surgical requirements. The supplementary medications administered to all patients included dexamethasone (5 mg), propacetamol (2 g), and palonosetron (0.25 mg).

After surgery, when patients awakened (MOAA/S ≥ 4), they were transferred to the Post-Anesthesia Care Unit (PACU) for continued monitoring. In the PACU, the Aldrete score was assessed every five minutes. Patients were discharged only upon achieving an Aldrete Score of at least nine, without significant adverse effects, such as nausea or dizziness.

Spontaneous breathing was maintained throughout the surgery. In cases of airway obstruction or hypoxemia, interventions such as jaw thrust or chin lift, insertion of oral airways, or bag mask ventilation were applied, with hypoxemia indicated by pulse oxygen saturation below 90%. Bradycardia is defined as a heart rate of less than 50 beats per minute and is treated with intravenous atropine (0.5 mg). Tachycardia is defined as a heart rate exceeding 100 beats per minute and is managed with fluid supplementation or intravenous administration of esmolol (20 mg). Hypotension is defined as a systolic blood pressure below 90 mmHg or a decrease of more than 20% from baseline, and treatment involves administration of ephedrine (6 mg). Hypertension is defined as a systolic blood pressure greater than 180 mmHg or an increase of more than 20% from baseline, with treatment including deepening anesthesia or intravenous administration of esmolol (20 mg). Body movement is defined as movement that interferes with the procedure, necessitating the use of sedatives to facilitate the surgery.

The patients provided information regarding their baseline characteristics during the preoperative interview. All information related to surgery and sedation, including surgical duration, sedation duration, types of anesthetic agents administered, MOAA/S scores, and adverse events, was documented by an anesthesiologist during sedation. Furthermore, physician satisfaction with sedation was assessed immediately after the procedure. Pain, nausea, and anesthesia satisfaction scores were evaluated either 30 min after arrival in the PACU or upon discharge, whichever occurred first. On the first postoperative day, between 8:00 AM and 9:00 AM, a follow-up questionnaire encompassing the pain score, nausea, anesthesia satisfaction, anxiety and depression scores, and sleep quality was sent to the patient via WeChat.

Outcomes

The primary endpoint was the immediate postoperative anesthesia satisfaction score. The ISAS consists of 11 questions, each with six potential responses used in this study. Responses were scored on a scale ranging from –3 to +3. The average score from the 11 questions constitutes the patient's final anesthesia satisfaction score.[30]

The secondary endpoints included (1) anesthesia satisfaction score on 1 day postoperatively; (2) the incidence of high-intensity injection pain (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain;[31] a score ≥ 2 indicates

high-intensity pain);[32] (3) sedation success rate (We define successful sedation as completing the procedure without needing rescue medication or exceeding five doses of either remimazolam or propofol [excluding remifentanil] within any consecutive 15-minute interval);[22,33] (4) pain scores immediately and 1 day postoperatively (Numeric Rating Scale [NRS]; ranges, 0–10; 0 representing no pain and 10 representing the worst pain); (5) nausea scores immediately and 1 day postoperatively (NRS; ranges, 0–10; 0 denoting none and 10 denoting very severe);[34] (6) time to being alert (from the initial drug administration to alertness [MOAA/S ≥ 4], and from the final drug administration to alertness [MOAA/S ≥ 4]); (7) length of the PACU stay (from PACU admission to discharge); (8) time to discharge (from the initial drug administration to discharge, and from the final drug administration to discharge); (9) clinician satisfaction (range, 1–5; 1 = extremely dissatisfied; 2 = moderately dissatisfied; 3 = neither satisfied nor dissatisfied; 4 = moderately satisfied, and 5 = extremely satisfied); (10) sleep quality on postoperative day 1 (NRS; ranges, 0–10, with 0 representing the best sleep quality and 10 representing the worst sleep quality);[35] (11) anxiety and depression score on postoperative day 1 (the Hospital Anxiety and Depression Scale [HADS]; range, 0–42; a score of 15 or higher signifies severe psychological distress).[36]

Statistical Analysis

Previous studies have established that a deviation of 0.6 on the ISAS is statistically significant.[30] In this study, we set the non-inferiority margin to –0.6.[37] Our preliminary data indicated that the immediate postoperative ISAS scores exhibited a standard deviation (SD) of 1.06. A sample size of 67 patients per group was required to establish non-inferiority with a one-sided α level of 0.025 and a power of 0.90. Considering an anticipated dropout rate of 20%, the final sample size was 84 participants per group.

The normality of the data was assessed using the Shapiro–Wilk test. Normally distributed data are presented as means (SD), while non-normally distributed data are reported as medians (interquartile ranges). Categorical data are presented as counts (percentages). The primary analysis used data from both randomized and per-protocol populations. Generalized estimating equations were used for the primary outcome, with standard errors computed using the robust method, and the working correlation structure was set as independent. The model included treatment, time point (categorical), and the interaction between treatment and time point as independent variables. The mean differences in immediate postoperative anesthesia satisfaction scores between the groups and their 97.5% CIs were derived from this model. Furthermore, the same model was used to estimate the mean differences and related CIs in the anesthesia satisfaction scores on postoperative day 1.

Subgroup analyses were performed to investigate the primary endpoint further. Subgroups were defined based on marital status (married vs unmarried), type of procedure (dilation and curettage vs other procedures), educational level (college level or higher vs below college level), preoperative combined HADS score (score ≥ 15 vs score < 15), preoperative anxiety HADS score (score ≥ 7 vs score < 7), preoperative depression HADS score (score ≥ 7 vs score < 7), and preoperative nausea score (score > 3 vs score ≤ 3). The mean differences and 95% CIs were estimated for each subgroup.

Secondary endpoint analysis were performed using the randomized population. Continuous variables were analyzed using generalized estimating equations, Mann–Whitney tests, or *t*-tests, whereas categorical variables were analyzed using the χ^2 test or Fisher's exact test. All analyses were performed using the R software (version 4.3.3). Except for the primary endpoint, all analyses were performed with a statistical significance level of $p < 0.05$.

Results

There were 200 patients in total enrolled for this study, of whom 168 were randomized: 84 were in the remimazolam group and 84 in the propofol group (Figure 1). Two patients in the remimazolam group received rescue medication but were still included in the final analysis. Ultimately, 168 patients were included in the randomized analysis, while 166 patients were included in the per-protocol analysis. Baseline data were comparable between the two groups (Table 1). The mean (SD) age was 31.0 (7.1) years and 134 (79.8%) of the 168 participants underwent dilation and curettage.

The details of the procedure and sedation are presented in Table 2 and Figure 2. During the sedation period, the proportion of time spent at MOAA/S scores of 0 or –1 was significantly lower in the remimazolam group than in the

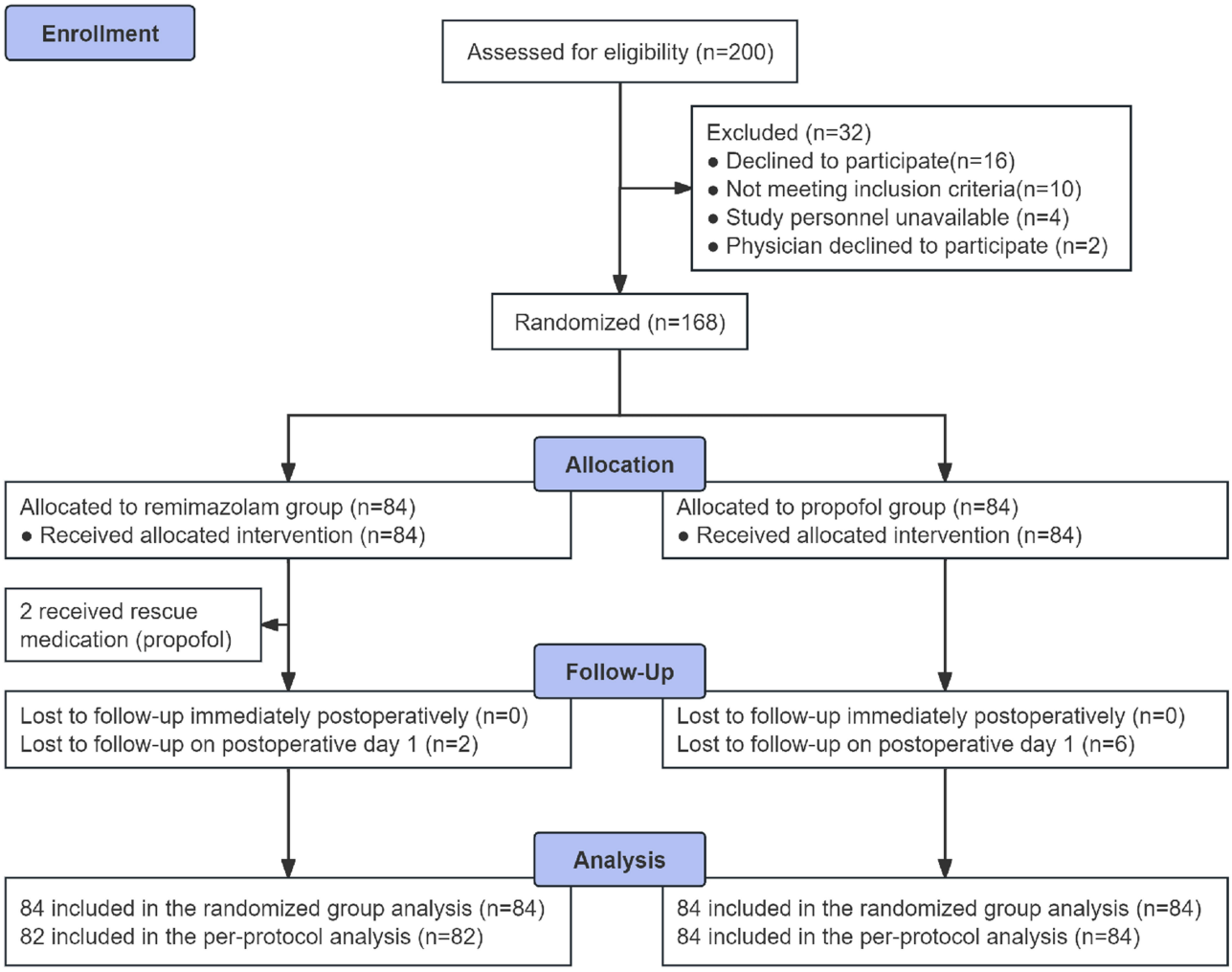

Figure 1 Participant Flow.

propofol group (50.1 [15.5] % vs 59.8 [9.0] %; difference, –9.6 [95% CI: –13.5 to –5.6] %; $p < 0.001$). The proportion of time spent at MOAA/S score of 2 was higher in the remimazolam group (17.2 [11.9] % vs 10.6 [9.1] %; difference, 6.6 [95% CI: 3.3 to 9.8] %; $p < 0.001$). Similarly, the proportion of time spent at MOAA/S score of 3 was higher in the

Table 1 Characteristics of Patients at Baseline

	Remimazolam group (n = 84)	Propofol group (n = 84)	P value
Age, mean (SD), y	31.5 (7.3)	30.5 (6.8)	0.35
Height, mean (SD), cm	163.4 (4.9)	163.0 (5.3)	0.60
Weight, mean (SD), kg	57.7 (8.1)	57.8 (8.9)	0.92
BMI, mean (SD), kg/m²	21.6 (2.9)	21.8 (3.3)	0.74
Education, Median (IQR), y	15.0 (12.8–16.0)	15.0 (12.0–16.0)	0.61
Preoperative combined HADS score, mean (SD)	10.4 (6.2)	11.1 (5.7)	0.48
Preoperative anxiety HADS score, mean (SD)	5.4 (3.5)	6.1 (2.8)	0.18

(*Continued*)

Table 1 (Continued).

	Remimazolam group (n = 84)	Propofol group (n = 84)	P value
Preoperative depression HADS score, mean (SD)	5.0 (3.2)	5.0 (3.4)	1
Type of surgery, No./total (%)			0.88
Dilation and curettage	68/84 (81.0)	66/84 (78.6)	
Diagnostic or operative hysteroscopy	15/84 (17.9)	16/84 (19.0)	
Other	1/84 (1.2)	2/84 (2.4)	
Marital status, No./total (%)			1
Married	55/84 (65.5)	55/84 (65.5)	
Unmarried	29/84 (34.5)	29/84 (34.5)	
Previous pregnancies, No./total (%)	59/84 (70.2)	60/84 (71.4)	1
Among those with previous pregnancies, No./total (%)			
Ever surgical abortion	40/84 (47.6)	35/84 (41.7)	0.53
Ever vaginal delivery	28/84 (33.3)	32/84 (38.1)	0.63
Ever cesarean delivery	21/84 (25.0)	18/84 (21.4)	0.71
Prior other gynecologic procedures, No./total (%)	14/84 (16.7)	9/84 (10.7)	0.37
Preoperative nausea score, mean (SD)	1.8 (2.1)	1.2 (2.0)	0.06
Preoperative sleep quality, mean (SD)	3.0 (2.1)	2.4 (1.9)	0.08

Notes: Data are expressed as mean (standard deviation), No./total (%), or median (interquartile range).
Abbreviations: BMI: Body Mass Index, IQR: Interquartile Range, SD: Standard Deviation, HADS: Hospital Anxiety and Depression Scale.

Table 2 Characteristics of Procedure and Sedation

	Remimazolam group (n = 84)	Propofol group (n = 84)	Absolute difference (95% CI)	P value
Sedation time, Median (IQR), min	11.5 (10.0–14.0)	11.0 (9.0–13.0)	0.5 (–1.0 to 2.0)	0.30
Procedure time, Median (IQR), min	7.0 (5.0–9.0)	6.5 (5.0–9.0)	0.5 (–1.0 to 2.0)	0.44
Administered dose of sedatives				–
Remimazolam, Median (IQR), mg	20.0 (17.5–22.5)	–		
Propofol, Median (IQR), mg	–	150.0 (140.0–180.0)		
Remifentanil, Median (IQR), μg	75.0 (70.0–90.0)	70.0 (60.0–80.0)	5.0 (0.0 to 10.0)	0.08
Times of top-up doses	1.5 (1.0–3.0)	1.0 (1.0–2.0)	0.5 (0.0 to 1.0)	0.14

Notes: Data are expressed as median (interquartile range).
Abbreviations: IQR: Interquartile Range, CI: Confidence Interval.

remimazolam group (14.3 [8.7] % vs 10.7 [7.7] %; difference, 3.6 [95% CI: 1.1 to 6.1] %; $p = 0.005$). However, the proportion of time spent at MOAA/S scores of 4 or 5 was comparable between the two groups (18.4 [5.4] % vs 18.9 [6.9] %; difference, –0.5 [95% CI: –2.4 to 1.4] %; $p = 0.6$). There were no significant differences in procedure time (7.0 [5.0–9.0] min vs 6.5 [5.0–9.0] min; difference, 0.5 [95% CI: –1.0 to 2.0] min; $p = 0.44$) or sedation time (11.5 [10.0–14.0] min vs 11.0 [9.0–13.0] min; difference, 0.5 [95% CI: –1.0 to 2.0] min; $p = 0.30$) between the two groups.

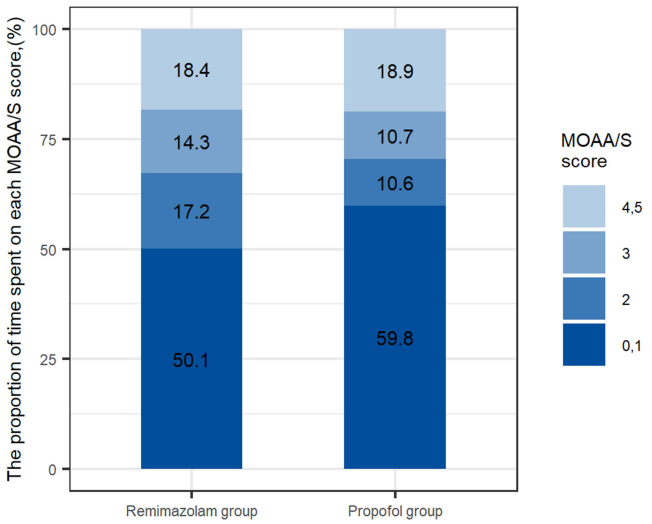

Figure 2 The proportion of time spent on each MOAA/S score during sedation.

Throughout the sedation period, no significant differences in the dosage of remifentanil (75.0 [70.0–90.0] μg vs 70.0 [60.0–80.0] μg; difference, 5.0 [95% CI: 0.0 to 10.0] μg; $p = 0.08$) were observed between the two groups, and the frequency of top-up doses (1.5 [1.0–3.0] vs 1.0 (1.0–2.0); difference, 0.5 [95% CI: 0.0 to 1.0]; $p = 0.14$) was similar.

In the randomized population, the mean (SD) ISAS scores immediately after surgery were 1.7 (0.6) in the remimazolam group compared to 2.0 (0.7) in the propofol group (unadjusted difference, –0.2; 97.5% CI: –0.5 to –0.0, $p = 0.02$). In the per-protocol analysis, the mean (SD) scores on the ISAS immediately postoperatively were 1.7 (0.6) in the remimazolam group compared to 2.0 (0.7) in the propofol group (unadjusted difference, –0.2; 97.5% CI: –0.5 to –0.0, $p = 0.02$). In both the randomized and per-protocol populations, the lower limit of the one-sided 97.5% CI satisfied the criteria for non-inferiority (margin of –0.6; Figure 3). In subgroup analyses, none of the characteristics significantly altered the effect of remimazolam on the primary outcome (Figure 3).

At postoperative day 1, the ISAS scores for the remimazolam and propofol groups were 1.9 (0.7) and 2.1 (0.6), respectively (difference, –0.1; 95% CI: –0.3 to 0.1, $p = 0.17$). High-intensity injection pain was less commonly observed in the remimazolam group than in the propofol group (3.6% vs 45.2%; difference, –41.7% [95% CI: –54.2% to –29.1%]; $p < 0.001$). The success rate of sedation was 97.6% in the remimazolam group and 100% in the propofol group (difference, –2.4%; 95% CI: –6.3% to 1.5%). While the immediate postoperative pain scores were not significantly different between the two groups of patients (2.4 [2.0] vs 2.6 [1.8]; difference, –0.2 [95% CI: –0.8 to 0.4]; $p = 0.50$), the remimazolam group exhibited higher pain scores than the propofol group on postoperative day 1 (1.1 [1.2] vs 0.7 [0.9]; difference, 0.4 [95% CI: 0.1 to 0.7]; $p = 0.02$). Postoperative nausea scores were significantly higher in the remimazolam group than in the propofol group, both immediately after surgery (0.7 [1.6] vs 0.2 [0.7]; difference, 0.5 [95% CI: 0.1 to 0.9]; $p = 0.01$) and on postoperative day 1 (0.9 [1.6] vs 0.4 [0.8]; difference, 0.5 [95% CI: 0.1 to 0.9]; $p = 0.01$). The remimazolam group exhibited a significantly prolonged PACU stay than the propofol group (27.6 [9.1] min vs 22.4 [7.0] min; difference, 5.2 [95% CI: 2.7 to 7.6] min; $p < 0.001$). The durations between the first and last drug administrations to discharge were significantly prolonged in the remimazolam group compared to those in the propofol group (41.7 [10.7] min vs 35.3 [8.7] min; difference, 6.4 [95% CI: 3.4 to 9.4] min; $p < 0.001$; 36.1 [10.7] min vs 29.6 [7.2] min; difference, 6.5 [95% CI: 3.7 to 9.3] min; $p < 0.001$). No significant differences were observed between the two groups in terms of the time from the first drug administration to be alert, the time from the last drug administration to be alert, or clinician satisfaction. Sleep quality scores were significantly higher in the remimazolam group than in the propofol group (4.2 [3.0] vs 2.5 [2.4]; difference, 1.8 [95% CI: 0.9 to 2.6]; $p < 0.001$). Anxiety HADS scores on postoperative day 1 were significantly higher in the remimazolam group compared to the propofol group (4.9 [3.3] vs 3.9 [2.7]; difference, 1.0 [95% CI: 0.1 to 2.0]; $p = 0.03$). Similarly, the depression HADS scores on postoperative day 1 were significantly higher in the remimazolam group than in the propofol group (4.9 [3.6] vs 3.6 [3.3]; difference, 1.3 [95% CI: 0.2 to 2.4]; $p < 0.02$, Table 3).

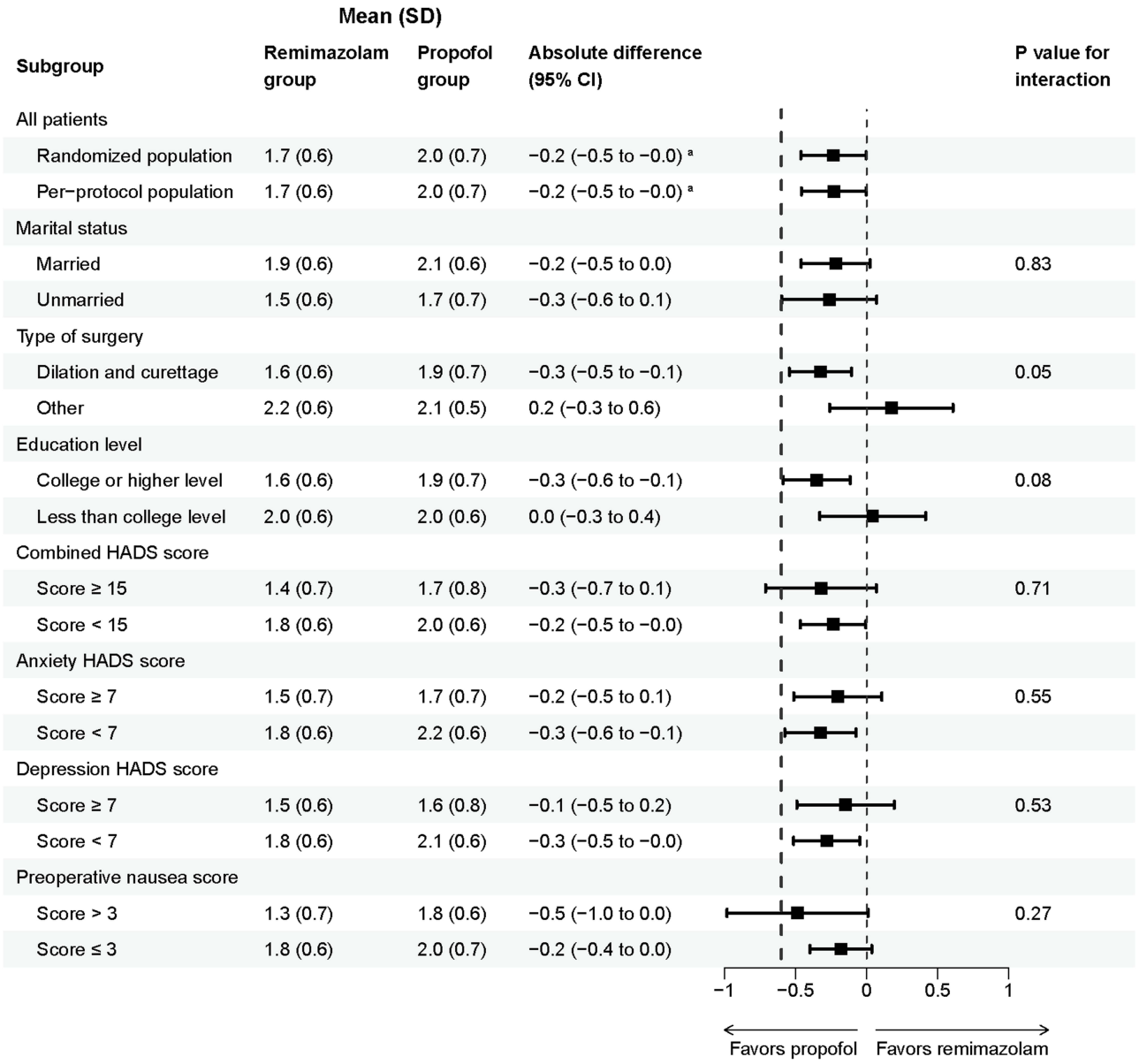

Figure 3 Primary outcome: mean (SD) ISAS scores immediately postoperatively in randomized and per-protocol populations, and subgroup analyses in the randomized population.
Notes: [a]The primary outcome is reported with a 97.5% confidence interval.

There was no significant difference in the incidence of intraoperative adverse events, including bradycardia, tachycardia, hypotension, hypertension, the composite of hypoxemia and airway intervention, and body movement between the two patient groups (Table 4).

Discussion

This randomized clinical trial, comparing anesthesia satisfaction between patients undergoing outpatient gynecological surgery with remimazolam or propofol sedation, demonstrated the non-inferiority of remimazolam to propofol.

Our study builds upon the existing evidence presented in previous studies. Two randomized controlled trials have demonstrated comparable sedation success rates between remimazolam and propofol in patients undergoing hysteroscopy,[38,39] consistent with the secondary outcome of our study. A primary distinction between our trial and these studies is that our study's primary outcome was patient anesthesia satisfaction. Moreover, our study population

Table 3 Primary and Secondary Outcomes

	Remimazolam group (n = 84)	Propofol group (n = 84)	Absolute difference (95% CI)	P value
Primary Outcome				
Patient satisfaction immediately postoperatively, mean (SD)	1.7 (0.6)	2.0 (0.7)	–0.2 (–0.5 to –0.0)[a]	0.02
Secondary Outcomes				
Patient satisfaction postoperative day 1, mean (SD)	1.9 (0.7)	2.1 (0.6)	–0.1 (–0.3 to 0.1)	0.17
High-intensity injection pain	3/84 (3.6)	38/84 (45.2)	–41.7 (–54.2 to –29.1)	< 0.001
The success rate of sedation, No./total (%)	82/84 (97.6)	84/84 (100.0)	–2.4 (–6.3 to 1.5)	0.50
Pain, mean (SD)				
Immediately postoperatively	2.4 (2.0)	2.6 (1.8)	–0.2 (–0.8 to 0.4)	0.50
Postoperative day 1	1.1 (1.2)	0.7 (0.9)	0.4 (0.1 to 0.7)	0.02
Nausea score, mean (SD)				
Immediately postoperatively	0.7 (1.6)	0.2 (0.7)	0.5 (0.1 to 0.9)	0.01
Postoperative day 1	0.9 (1.6)	0.4 (0.8)	0.5 (0.1 to 0.9)	0.01
Time to be alert, mean (SD), min				
From the final administration of drugs	6.3 (1.9)	6.0 (1.3)	0.3 (–0.2 to 0.8)	0.22
From the first administration of drugs	12.0 (3.1)	11.8 (4.1)	0.2 (–0.9 to 1.3)	0.77
Length of the PACU stay, mean (SD), min	27.6 (9.1)	22.4 (7.0)	5.2 (2.7 to 7.6)	< 0.001
Time to discharge, mean (SD), min				
From the final administration of drugs	36.1 (10.7)	29.6 (7.2)	6.5 (3.7 to 9.3)	< 0.001
From the first administration of drugs	41.7 (10.7)	35.3 (8.7)	6.4 (3.4 to 9.4)	< 0.001
Clinician Satisfaction, Median (IQR)	4.0 (3.0–4.0)	4.0 (3.8–4.0)	0.0 (–0.5 to 0.0)	0.06
Sleep quality on postoperative day 1, mean (SD)	4.2 (3.0)	2.5 (2.4)	1.8 (0.9 to 2.6)	< 0.001
Anxiety HADS score on postoperative day 1, mean (SD)	4.9 (3.3)	3.9 (2.7)	1.0 (0.1 to 2.0)	0.03
Depression HADS score on postoperative day 1, mean (SD)	4.9 (3.6)	3.6 (3.3)	1.3 (0.2 to 2.4)	0.02

Notes: Data are expressed as mean (standard deviation), No./total (%), or median (interquartile range). [a]The primary outcome is reported with a 97.5% confidence interval.
Abbreviations: IQR, Interquartile Range, SD, Standard Deviation, HADS, Hospital Anxiety and Depression Scale, CI, Confidence Interval, PACU, Post-Anesthesia Care Unit.

included not only patients undergoing hysteroscopic examinations but also those undergoing hysteroscopic surgeries and dilation and curettage procedures. Additionally, two randomized controlled trials revealed a superior safety profile of remimazolam compared with propofol,[11,40] whereas our study identified no significant difference in adverse event rates. Possible explanations for these divergent study outcomes include including younger patients, which could have mitigated the disparity in adverse event rates between the two groups, and sample size determination based on the primary study endpoint, which might have been insufficient for identifying underlying differences.

To evaluate the robustness of the results, subgroup analyses were performed based on prospectively defined categories. The analysis revealed no interaction effect between treatment assignment and subgroups, suggesting that the effects of remimazolam and propofol on patient anesthesia satisfaction are consistent across various subgroups. However, we acknowledge that this analysis may be underpowered and should be considered exploratory.

Table 4 Incidence of Treatment-Related Adverse Events

	Remimazolam group (n = 84)	Propofol group (n = 84)	Absolute difference (95% CI)	P value
Bradycardia, No./total (%)	0/84	0/84	–	–
Tachycardia, No./total (%)	4/84 (4.8)	0/84 (0.0)	4.8 (–0.5 to 11.6)	0.12
Hypotension, No./total (%)	1/84 (1.2)	7/84 (8.3)	–7.1 (–14.7 to 0.4)	0.07
Hypertension, No./total (%)	4/84 (4.8)	5/84 (6.0)	–1.2 (–9.2 to 6.8)	1
Hypoxia/airway intervention, No./total (%)	23/84 (27.4)	31/84 (36.9)	–9.5 (–24.8 to 5.7)	0.19
Body movement, No./total (%)	7/84 (8.3)	8/84 (9.5)	–1.2 (–11.0 to 8.6)	0.79

Notes: Data are expressed as No./total (%).
Abbreviation: CI, Confidence Interval.

We selected patient anesthesia satisfaction as the primary endpoint of our study because of its importance in evaluating sedation comprehensively.[41] The increasing focus on patient-centered outcomes supports using these measures in perioperative research.[42] The ISAS was used in our study to assess patient satisfaction with anesthesia. ISAS, designed to evaluate satisfaction among patients receiving monitored anesthesia care (MAC), has been widely used in various research contexts.[37,43–46]

Our study indicates that remimazolam is associated with prolonged discharge time compared to propofol for sedation in patients undergoing outpatient gynecological surgery. However, no significant differences were observed in the time required to regain full alertness. These findings partially contrast with a meta-analysis, which indicated that remimazolam and propofol demonstrate equivalent time to full alertness and discharge for sedation in gastrointestinal endoscopies.[47] This observed variation could be attributed to differences in the discharge criteria of PACUs among various medical centers. In addition to adhering to a standard Aldrete Score of at least 9, our institution emphasizes the absence of significant adverse effects, such as nausea or dizziness. Notably, patients in the remimazolam group in our study reported higher postoperative nausea scores, which may have contributed to the prolonged discharge time.

Our study indicates that the remimazolam group exhibited higher pain and nausea scores on postoperative day 1. However, anesthesia satisfaction levels were comparable between the two groups. There are two possible reasons for this. First, although the remimazolam group reported higher pain and nausea scores, it is important to note that postoperative anesthesia satisfaction is assessed across eleven dimensions. Second, both groups experienced mild pain (NRS score ≤ 3) and mild nausea (NRS score ≤ 3),[34,48] which suggests that the negative impact on satisfaction from pain and nausea was minimal.

The incidence of hypoxemia in this study was higher than previously reported.[11] This discrepancy may be attributed to several factors. We assessed hypoxemia using composite endpoints, which included both the occurrence of hypoxemia and the necessity for airway intervention. Consequently, some patients who required airway intervention but did not experience hypoxemia were included in our analysis. It is important to note that these patients may not have developed hypoxemia even in the absence of airway intervention. Furthermore, deeper levels of sedation have been associated with an increased incidence of hypoxemia, which may also contribute to our findings.

Consistent with previous investigations, our study observed a decreased occurrence of injection pain with remimazolam compared to propofol.[19] However, the two groups observed no significant differences in immediate postoperative pain or operator satisfaction. Interestingly, on postoperative day 1, remimazolam was associated with increased anxiety, depression, sleep quality, pain, and nausea scores, which warrants further investigation.

Our study has several limitations. First, it was a single-center study. Consequently, validation through multicenter studies is warranted to increase the generalizability of our findings. Second, although anesthesiologists were aware of patient group assignments, we ensured that the outcome evaluators were blinded to the randomization allocation to

minimize bias. Third, the enrolled patients did not adequately represent the population, as they primarily underwent procedures such as dilation and curettage and diagnostic or operative hysteroscopy, which may restrict the extrapolation of our findings. Fourth, the results of this study are only applicable to short procedures in the outpatient department, indicating certain limitations. Finally, our study used deeper levels of sedation influenced by local practice, potentially limiting the generalizability of our results.

Conclusion

Remimazolam demonstrates non-inferiority to propofol in terms of anesthesia satisfaction among patients undergoing outpatient gynecological surgery. Therefore, it should be considered as a new sedation alternative in such procedures.

Data Sharing Statement

All data produced or analyzed during this study were available in the published article. Further inquiries regarding the datasets can be addressed to the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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