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ARTICLE

Remimazolam versus propofol in combination with esketamine for surgical abortion: A double-blind randomized controlled trial

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Abstract

Remimazolam is a new benzodiazepine with a short half-life, good efficacy, and safety profiles in general anesthesia. Combining esketamine with propofol (P + E) could reduce propofol consumption and injection pain. It is, however, unclear if a low dose of remimazolam co-administrated with esketamine (R + E) is comparable to the increasingly used P + E for surgical abortion with general anesthetic. We conducted a double-blind randomized controlled trial to compare the efficacy and safety of R + E and P + E. Two hundred patients scheduled for a surgical abortion were randomized to receive remimazolam 0.3 mg/kg plus esketamine 0.3 mg/kg (R + E), and propofol 2 mg/kg plus esketamine 0.3 mg/kg (P + E). Sedative effectiveness was evaluated by measuring the time to lose consciousness (LOC), recovery time, and successful sedation rate. Safety was assessed by hemodynamics and adverse events during and postoperation. The time to LOC and recovery time in R + E was 5 s shorter and 1 min longer than that in P + E, respectively (both $p < 0.001$). Success sedation rate did not differ between groups ($p = 0.73$). Bradycardia incidence and injection site pain were less frequent in the R + E group than that in the P + E group. More rash was observed in the R + E group compared with the P + E group (32% vs. 5%, $p < 0.001$), but all were mild (only chest rash) and resolved subsequently. Low dose of remimazolam when combined with esketamine has favorable profiles with rapid onset and recovery, but mild hemodynamic side effects and adverse events. It can be used as an alternative for surgical abortion with general anesthetic.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The combination use of remimazolam/esketamine (R + E) has been proved to have shorter awakening time and fewer adverse events compared with propofol

Linli Yue and Xiaoling Ma contributed equally to this work and share first authorship.

co-administrated with other analgesics. Esketamine is increasingly used in combination with propofol (P + E), to reduce propofol consumption and propofol-induced injection pain.

WHAT QUESTION DID THIS STUDY ADDRESS?

Whether low dose of R + E would have a comparable efficacy and safety profile with faster onset compared to P + E in patients undergoing surgical abortion.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Low dose of R + E presented a shorter onset but longer recovery time compared to P + E. Bradycardia and injection site pain were less frequent while rash was more common in patients receiving R + E, although all rashes were mild and resolved subsequently.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Because of its efficacy and safety profile, remimazolam can facilitate quick completion of routine procedures with low risk of deep or prolonged sedation.

INTRODUCTION

Induced abortion with medical or surgical methods is a common health intervention to end a pregnancy.[1] It is estimated that globally, 60% of women with unwanted pregnancy chose induced abortion for pregnancy termination each year.[2] Surgical abortion is one of the methods to terminate a pregnancy within 14 weeks, but it may cause considerable pain and discomfort to the patients.[3] Surgical abortion with general anesthetic, however, substantially lowers the frequency of peri-operative adverse events, minimizes the pain and discomfort, and improves patient's satisfaction.[4] It is increasingly used in clinical practice.[5]

Current surgical abortion with general anesthetic includes the administration of propofol, which has a rapid onset of action (15–40 s) and a short half-life (30–60 min).[6,7] However, adverse events, especially respiratory depression, hypoxia, hypotension, and pain at the injection site, have long been recorded in deep sedation of propofol, in a dose-dependent manner.[8–10] Remimazolam, a new ester-based benzodiazepine, is quickly metabolized into inactive metabolites by tissue esterases.[11,12] It increases the activity of γ-subunit-containing GABAA receptors, which starts cell membrane hyperpolarization and inhibits neural activity by increasing chloride in-flux.[13–15] Remimazolam has a short (45 min) and low context-sensitive half-life (where context refers to the infusion duration), meaning that its half-life is not significantly influenced by the duration of infusion.[16] This feature enables rapid metabolism even with a longer infusion,[16] thus providing more predictable sedation.[17] It has been shown to be well-tolerated and effective for general anesthesia when used alone or in combination with analgesics, with fewer adverse events compared with propofol[18–20] and other benzodiazepines.[21,22] It does not cause respiratory depression or injection pain and has no significant impact on hemodynamics as propofol does.[17,23] It was reported to reduce stress during painless gastrointestinal endoscopy as well.[24] Remimazolam was approved for general anesthesia in South Korea and Japan, and procedural sedation in China, the United States, and Europe in adults.[16] With a high clearance rate, a short and low context-sensitive half-life, rapid onset and recovery time, and low liability for cardiorespiratory depression and injection pain, remimazolam appears to have several advantages over propofol.

Ketamine, an N-methyl-D-aspartic acid receptor antagonist, has been used in clinical settings as anesthetic analgesic since the 1960s.[25] Esketamine, a (S)-enantiomer of ketamine, has a stronger anesthetic effect than regular ketamine but fewer adverse effects.[26–28] However, esketamine alone may cause nausea, vomiting, and seizures.[29] The use of esketamine was approved in China in 2020[30] and it is increasingly used in combination with propofol (P + E) for procedural sedation to reduce propofol consumption[31,32] and the adverse events, such as propofol-induced injection pain.[28,33] Due to its analgesic properties, esketamine can potentially alleviate pain experienced by patients during surgical abortion, minimizing pain-induced body movements, and fluctuations in hemodynamics during the procedure. Remimazolam co-administrated with esketamine (R + E) could provide both effective sedation and analgesia for routine outpatient procedures, which could be an alternative to the increasingly used P + E. The combination use of R + E has been shown to have better profiles over propofol co-administered with sufentanil[34] and fentanyl[35] for procedures like gastroscopy

and endoscopy. These include shorter awakening time, lower postoperative pain scores, and fewer adverse effects on patients' respiratory and circulatory systems. However, it is unclear if R+E is comparable to P+E. Therefore, the primary objective of the current trial was to compare the efficacy and safety of P+E with low dose of R+E in patients undergoing surgical abortion. We hypothesized that R+E would have a comparable efficacy and safety profile with faster onset compared to P+E.

METHODS

Study design

This study was a double-blind, randomized controlled trial. This study was approved by the Medical Ethics Committee of Maternal and Child Health Hospital of Hubei Province (Ref No. 2022IEC102). Written informed consent was obtained from all participants before their enrollment. The study protocol was registered at clinicaltrials.gov (NCT05635955) and protocol has not changed or been amended after the trial started. This trial was conducted in line with the Declaration of Helsinki and adhered to relevant CONSORT guidelines.

Participants

Participants were recruited from an outpatient clinic in the Maternal and Child Health Hospital of Hubei Province who were scheduled for surgical abortion from August 1, 2022, to September 30, 2022. Inclusion criteria were (1) early intrauterine pregnancy less than 12 weeks confirmed by transabdominal ultrasound and human chorionic gonadotropin blood test, (2) aged 18–65 years old, (3) the American Society of Anesthesiologists (ASA) physical status ranked I–II, and (4) be able to provide informed consent. The patients were excluded from the trial when they had any of the following conditions: chronic pain, psychiatric disorders, liver or kidney failure, severe metabolic disorders, including diabetes, poor respiratory functions (with oxygen saturation level below 90%), and cardiovascular diseases, including hypertension and coronary heart disease. Patients who were taking psychotropic drugs that could potentially affect the effects of the investigational drugs were also excluded.

Randomization and blinding

All eligible patients were randomly allocated to two study arms (R+E and P+E) using computer-generated random numbers at a ratio of 1:1 by a medical professional who was not involved in the trial. Before the sedatives were administered, the study investigator (one senior anesthesiologist) opened the opaque envelopes that contained the random numbers to receive instructions for the procedure. All participants, the gynecologists who performed the abortion surgery, and the research anesthesiologist who collected the data were masked to the groups' allocations until the end of the trial.

Intervention

Prior to the procedures, all patients fasted from food for 8 h. Clear liquids were permitted up to 2 h prior to anesthesia. Upon entering the room, routine monitoring procedures, including electrocardiogram, heart rate (HR), oxygen saturation (SpO_2), and mean arterial pressure (MAP) was conducted. The patient was in the lithotomy position and the head was tilted to her right. Oxygen was then administered through a nasal cannula at a flow rate of 4 L/min.

Intravenous (i.v.) access was established 20 min before surgery. The specifications of remimazolam that we used are 36 mg per vial (free base). The drug was reconstituted according to the package insert, which involves adding 36 mL of sodium chloride 9 mg/mL (0.9%) solution to each vial, resulting in a final concentration of 1 mg/mL of remimazolam in 36 mL. The necessary dosage was then drawn into a syringe for administration. In the P+E group, i.v. anesthesia was first induced with 0.3 mg/kg esketamine followed by 2 mg/kg propofol (1%), slow injection over 1 min. In the R+E group, i.v. anesthesia was first induced with 0.3 mg/kg esketamine followed by 0.3 mg/kg remimazolam tosilate, slow injection over 1 min. All patients received a single injection of the investigational drugs during induction period. Peak sedation was expected to occur within 3–5 min, enabling a profound level of sedation during curettage, followed by rapid recovery after the procedure.

Throughout the abortion surgery, the modified observational alertness/sedation assessment score (MOAA/S, range from 0 to 5, with 5 as awake or minimally sedative and 0 as the deepest level of sedation) was used to assess sedation levels[36] once per minute. The procedure commenced when patients lost consciousness (LOC; defined as a MOAA/S score of 0). Time to LOC was recorded from the start of injection continuously until the patient's MOAA/S score reached 0. If the MOAA/S scores were greater than or equal to 1 or if there were any body movements, additional i.v. doses of 0.25 mg/kg propofol and 0.2 mg/kg remimazolam were administered. The supplemental doses were based on drug package inserts and standard clinical practice, and the

number of doses administered was recorded. The minimum required supplemental doses were given after the first dose to avoid affecting patient recovery due to the short duration of the procedure.

Any anesthesia-related adverse events were recorded and managed according to our hospital's treatment protocols. The adverse events included: respiratory depression (defined as $SpO_2 < 90\%$), hypotension (defined as systolic arterial pressure ≤ 80 mmHg, or systolic blood pressure decrease >20% compared to baseline), hypertension (defined as blood pressure ≥ 139/95 mmHg, or blood pressure increase >20% compared to baseline), bradycardia (defined as decrease in HR < 60/min), tachycardia (defined as increase in HR > 100/min), number of body movements, injection site pain, rash, and nausea and vomiting. Injection site pain was measured using a four-level pain scale (grades 0–3, 0 no pain, 1 mild pain, 2 moderate pain, and 3 severe pain). Patients were continuously asked about their level of pain by the anesthesiologist until LOC occurred. Grade above 0 was considered to have injection site pain. Hypotension and bradycardia were managed by i.v. ephedrine 3–6 mg/kg or i.v. atropine 0.3–0.5 mg/kg, or by accelerating the infusion rate of sedation. Mild to moderate rash to sedative agents were treated with 10 mg Dexamethasone injection.

Peri-operative changes of vital signs, including MAP and HR, at each timepoint, including the entry into the operation room (T0), in sedation when vaginal dilator was placed (T1), in sedation when curettage began (T2), and postoperative awakening (T3) were recorded. The recovery from anesthesia was assessed using the Modified Aldrete Score, with scores recorded every 3 min after the operation until a recovery index of 9 or higher was reached. The recovery time was measured from the end of the last dose to the time when the MOAA/S score was greater than or equal to 3. Pain levels were evaluated using the postoperative Visual Analogue Scale (VAS) pain score, which ranged from 1 to 3 for mild pain, 4 to 6 for moderate pain, and 7 to 10 for severe pain.

A senior obstetrician-in-charge and a senior anesthesiologist who was responsible for anesthesia carried out all surgical abortion procedures according to our standard clinical practice. A research anesthesiologist collected relevant clinical data. All drugs were discontinued when the procedure was completed.

Outcomes

The primary outcome of the current study was sedative effect in terms of time to LOC (defined as MOAA/S score = 0). Secondary outcomes included sedative effect in terms of recovery time and success rate of sedation (measured by completing the induction of anesthesia without an additional dosage), the peri-operative changes in vital signs (HR and MAP), occurrence of peri+operative adverse events, including respiratory depression, bradycardia, hypotension, hypertension, number of body movements, injection site pain, and nausea and vomiting. The total additional dose, surgery time, and postoperative pain (VAS score at awakening) were also determined.

Sample size estimation

During the development of the study protocol, no previous studies were found using the same study drugs for sample size determination. Based on our previous experience and our hospital's observational data, we expected a difference in time to LOC of 3 s (38.5 s and 41.5 s for R + E and P + E group, respectively), that is, an effect size (Cohen's *d*) of 0.4, between the two groups. To achieve a statistical power of 80% with a two-sided type I error rate of 0.05, and a 1:1 ratio, a sample size of 100 patients in each group was estimated. Because all patients received the surgery as a day-care outpatient procedure without hospital admission, no follow-up was necessary, and loss of follow-up was not considered in the sample size calculation. Sample size estimation was performed using GPower (version 3.1.9.4).

Statistical analysis

Statistical analysis was conducted with Stata 14.0 (StataCorp.[37]). Continuous variables are presented as mean with SD, or median with interquartile range as appropriate. Categorical variables are expressed as *N* (%) of patients. The Student's *t*-test and the Mann–Whitney test were used to compare normally and non-normally distributed continuous variables, respectively. The Chi-square test and Fisher's exact test were used to compare categorical variables, as appropriate. Paired *t*-test and Wilcoxon signed rank test was used to test the difference of repeated measurements within each group. A two-sided *p* value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 207 patients were evaluated for eligibility by inclusion and exclusion criteria. Seven patients were excluded due to arrhythmia ($n = 4$), hyperthyroidism ($n = 1$), moderate anemia ($n = 1$), and myasthenia gravis ($n = 1$). The remaining 200 patients were randomly allocated to two study arms (Figure 1).

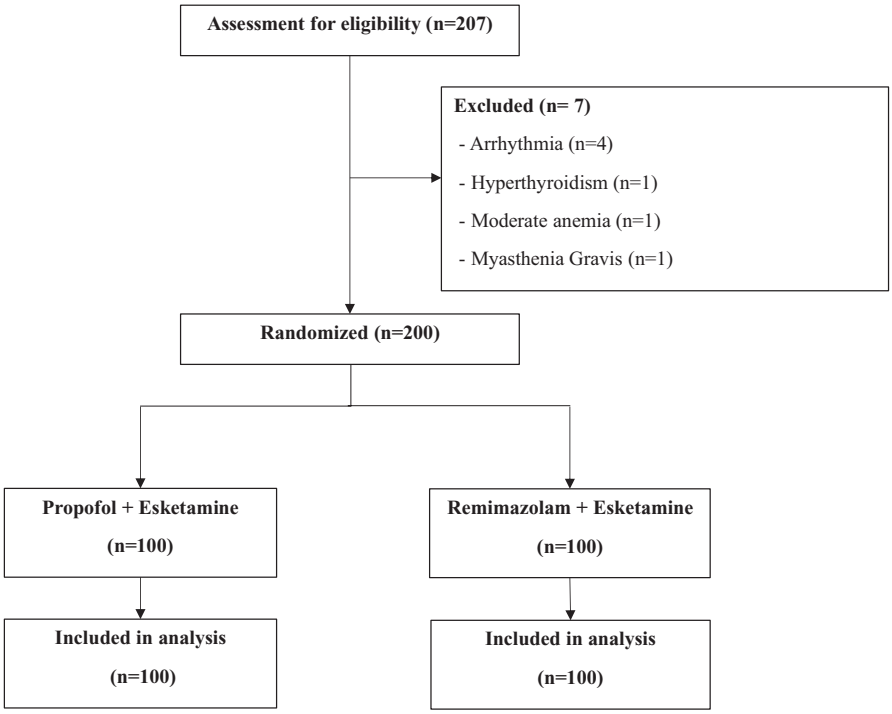

FIGURE 1 Patient recruitment and randomization flowchart. Between August 1 and September 30, 2022, a total of 207 patients were evaluated for eligibility by inclusion and exclusion criteria. Seven patients were excluded and the remaining 200 patients were randomly allocated to two study arms. All of the 200 participants were included in the final analysis of the trial.

The baseline demographic and clinical characteristics of patients, including age, body mass index, HR, and MAP, did not differ significantly between the two groups (Table 1). More patients in the P + E group were scheduled for hysteroscopic-induced abortion (induced abortion led by hysteroscope) than the R + E group (91% vs. 70%, standardized difference = 0.54, tested using STATA command STDDIFF[38]).

TABLE 1 Baseline characteristics.

	P + E $n = 100$	R + E $n = 100$
Age, years	30 (20–53)	31 (19–41)
BMI, kg/m^2	20.8 (16.4–26.6)	20.7 (16.9–26.0)
Heart rate, mmHg	76.5 (55–105)	75 (59–97)
Mean arterial pressure, bpm	84 (72–102)	84 (69–102)
Type of surgery		
Hysteroscopic induced abortion	91 (91.0%)	70 (70.0%)
Induced abortion	9 (9.0%)	30 (30.0%)

Note: Data are presented as median (interquartile range) or *n* (%) if stated otherwise.

Abbreviations: BMI, body mass index; P + E, propofol + esketamine; R + E, remimazolam + esketamine.

Evaluation of sedative effect

Primary outcome: The R + E group had a mean time to LOC of 37.0 s (95% confidence interval [CI]: 35.0–38.0), which was 5 s shorter than that of the P + E group (42.0 s, 95% CI: 40.0–43.0, $p < 0.001$; Table 2).

Secondary outcomes: The median recovery time of the R + E group (9 min), however, was 1 min longer than that of the P + E group (8 min, $p < 0.001$; Table 2). The successful sedation rate did not differ between the groups (81% vs. 71% for P + E and R + E, respectively, $p = 0.73$; Table 2). There were no significant differences between the two groups in terms of surgery duration, number of supplemental doses, or postoperative VAS pain score (Table 2).

Hemodynamic results

At T1, T2, and T3, the HR levels were significantly lower in the P + E group compared with that in the R + E group ($p < 0.001$; Figure 2a). The HR level increased significantly at T1 from T0 for both groups (8.5% increase for P + E vs. 24% increase for R + E) after induction ($p < 0.001$ for both increases; Figure 2b). It dropped significantly at T3 and T4 to below the level at T0 for P + E but not for R + E (Figure 2b). No significant differences were found in the MAP level at any observed timepoint between the two groups (Figure 3a). Both groups experienced a significant drop in MAP levels at T1 from T0, followed by a significant increase at T2 and T3 to levels above those at T0 (Figure 3b).

TABLE 2 Anesthesia-related indices.

	P + E $n = 100$	R + E $n = 100$	p Value
Anesthesia induction time, s			<0.001
Mean (95% CI)	42 (40–43)	37 (35–38)	
Recovery time, min			<0.001
Median (range)	8 (3–15)	9 (4–15)	
Successful rate of sedation	81 (81%)	78 (78%)	0.73
Duration of surgery, min	5 (2–10)	5 (3–11)	0.94
Number of supplemental doses			
1	18 (18.0%)	20 (20.0%)	0.78
2	1 (1.0%)	2 (2.0%)	
VAS pain score	1 (1–3)	1 (1–3)	0.99

Note: Data are presented as median (interquartile range) or *n* (%), if stated otherwise. Significance was tested by Mann–Whitney *U* test, *t*-test, chi-square test, and Fisher's exact test as appropriate.

Abbreviations: CI, confidence interval; P + E, propofol + esketamine; R + E, remimazolam + esketamine; VAS, Visual Analogue Scale.

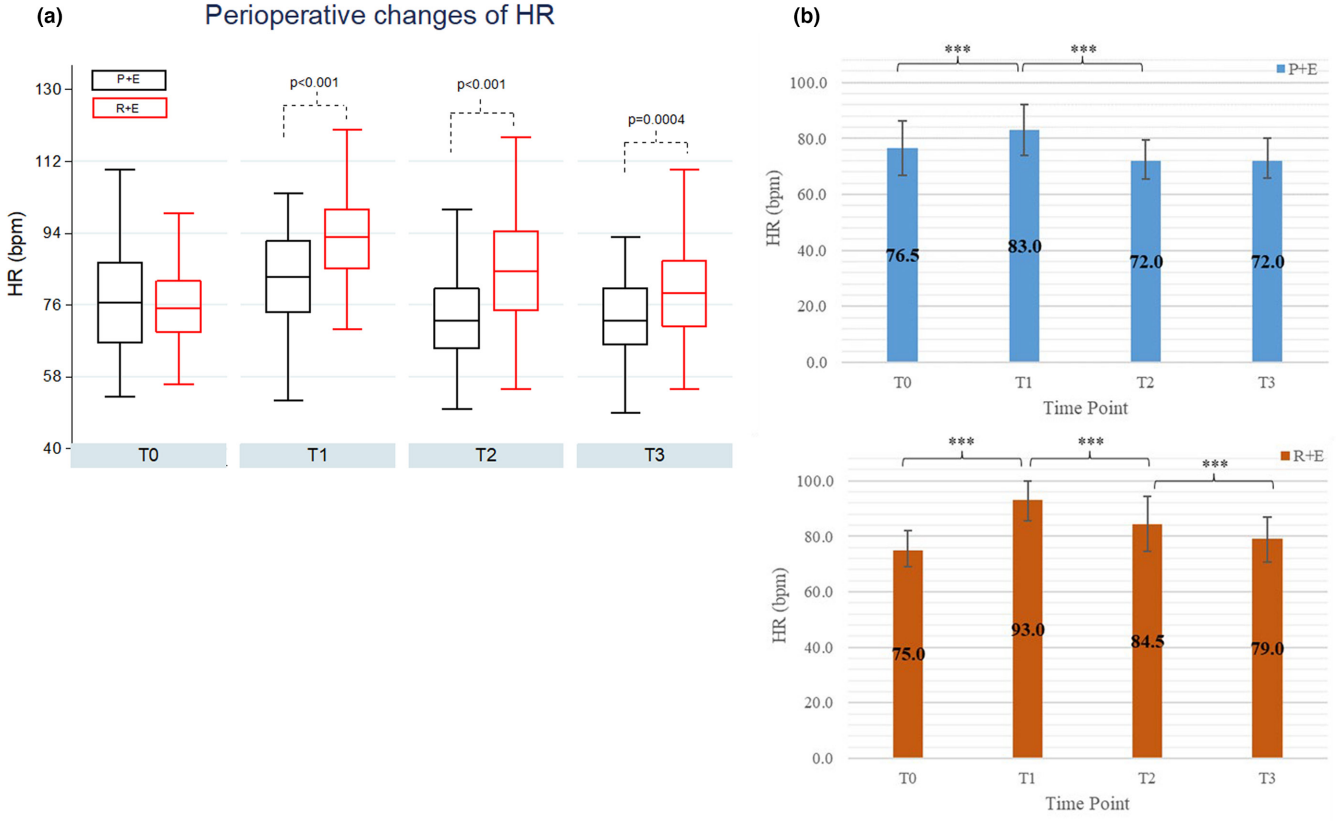

FIGURE 2 Peri-operative changes of HR between and within the groups. (a) Peri-operative changes between groups. (b) Peri-operative changes for each group. Values are median and vertical bars are first and third quartiles. *** $p < 0.001$, significance was tested by Mann–Whitney test for between group difference, Wilcoxon signed rank test for within group difference. HR, heart rate; P + E, propofol + esketamine; R + E, remimazolam + esketamine; T0, entry into the operation room; T1, in sedation when vaginal dilator placed; T2, in sedation when curettage began; T3, postoperative awakening.

Adverse events

No fatal or serious adverse events were reported during the surgery in any groups. A total of 52 and 82 adverse events were recorded during the whole abortion procedure in the P + E group and the R + E group, respectively ($p < 0.001$). This included 10% ($n = 5$) and 40% ($n = 33$) of rash incidence in each group respectively (Table 3), with

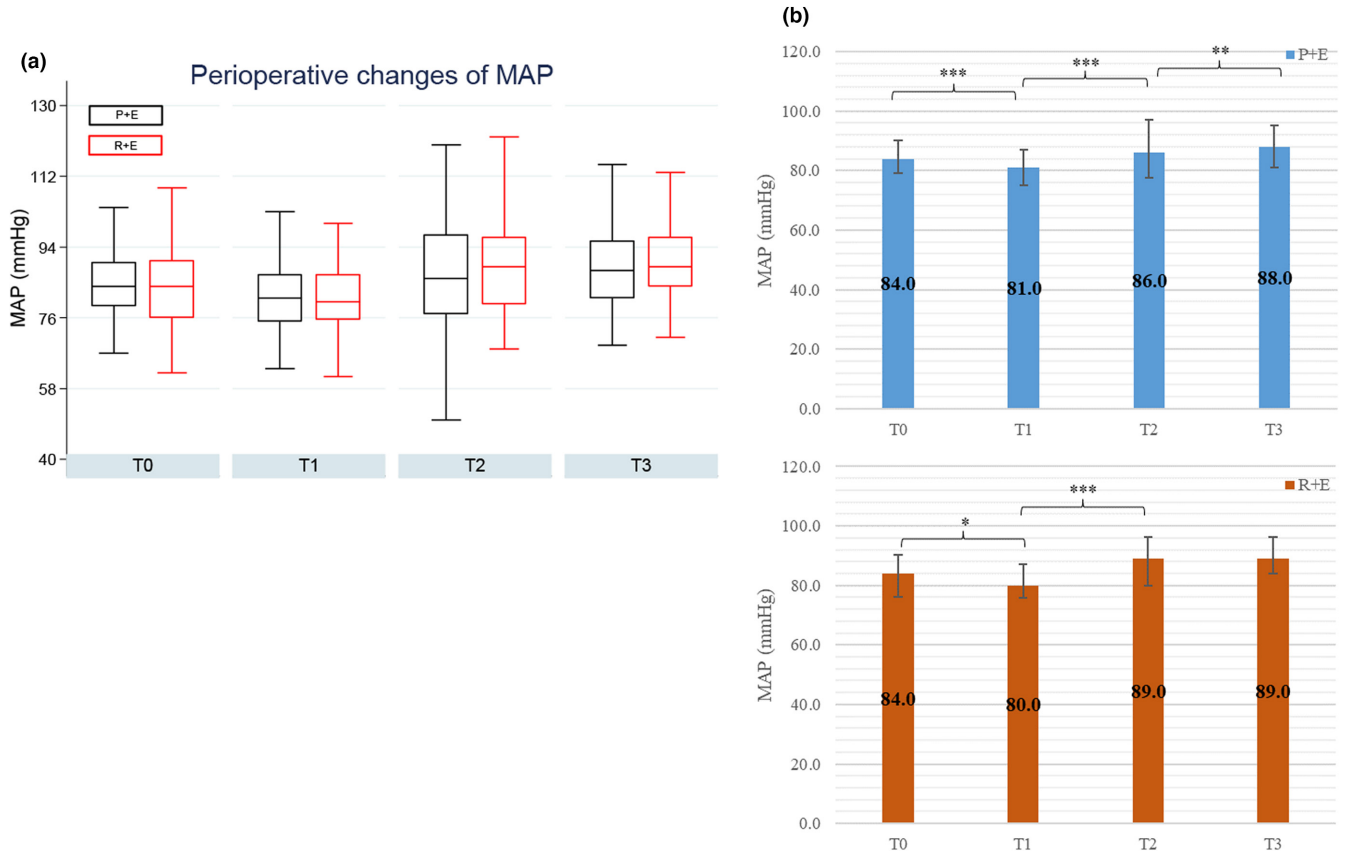

FIGURE 3 Perioperative changes of MAP between and within group. (a) Peri-operative changes between groups. (b) Peri-operative changes for each group. Values are median and vertical bars are first and third quartiles. ***$p < 0.001$ **$p < 0.01$ *$p < 0.05$, significance was tested by Mann–Whitney test for between group difference, Wilcoxon signed rank test for within group difference. HR, heart rate; MAP, mean arterial pressure; P + E, propofol + esketamine; R + E, remimazolam + esketamine; T0, entry into the operation room; T1, in sedation when vaginal dilator placed; T2, in sedation when curettage began; T3, postoperative awakening.

all being mild (only chest rash) and resolved with 10 mg Dexamethasone injection. Bradycardia occurred significantly less frequently in the R + E group compared to the P + E group during induction (0% vs. 6%, $p = 0.03$). Although not statistically significant, injection site pain appeared to occur more frequently in the P + E group than in the R + E group (9% vs. 2%, $p = 0.06$). Significantly more rash was observed in the R + E group compared with the P + E group (32% vs. 5%, $p < 0.001$). No significant differences were observed between groups in the occurrence of respiratory depression, hypertension, and hypotension. After induction, the most common adverse events observed was nausea and vomiting, and it occurred more often in the R + E group than in the P + E group (8% vs. 2%, $p = 0.05$).

DISCUSSION

Remimazolam has been studied in clinical trials as a sedative for procedural sedation, with most trials focusing on diagnostic procedures such as endoscopy, colonoscopy, gastroenteroscopy,[20,34,39–42] and hysteroscopy.[43,44] Among them, only a few compared remimazolam to propofol.[39,40,43,44] To our best knowledge, our randomized clinical trial was the first to compare remimazolam to propofol co-administrated with esketamine in surgical abortion. We found that a low dose of R + E presented a significantly shorter sedation induction but a longer recovery time compared to P + E. The HR was significantly higher across all the observed timepoints after sedation in the R + E group than that in the P + E group, whereas there was no significant difference in MAP. Our safety assessment showed that although R + E had more reported adverse events than P + E, patients receiving R + E experienced less injection site pain and bradycardia.

Chen et al.[39] and Chen et al.[40] demonstrated high sedation success rates for remimazolam in patients undergoing colonoscopy and endoscopy, that were statistically noninferior (96.9% and 97.3%, respectively) but numerically lower than those for propofol (100% in both studies). Our trial showed a similar trend, with sedation success rates that did not differ between groups but were numerically lower in the remimazolam group (78% vs. 81% for

TABLE 3 Adverse events observed.

	P + E $n = 100$	R + E $n = 100$	p Value
Overall reported AEs	52	82	<0.001
During induction			
Body movements	20	21	0.99
Injection site pain	9	2	0.06
Rash	5	32	<0.001
Respiratory depression	4	4	0.99
Bradycardia	6	0	0.03
Hypertension	2	6	0.28
Hypotension	2	0	0.5
Hiccough	0	5	0.06
Nausea and vomiting	0	1	0.99
Post-induction			
Rash	0	1	0.99
Hypertension	2	2	0.99
PONV	2	8	0.05

Note: Significance was tested by chi-square test and Fisher's exact test as appropriate.

Abbreviations: AE, adverse event; P + E, propofol + esketamine; PONV, postoperative nausea and vomiting; R + E, remimazolam + esketamine.

remimazolam and propofol, respectively). One phase II trial in 100 patients undergoing upper gastrointestinal endoscopy, showed that the success rates was positively associated with doses of remimazolam administrated (32%, 56%, and 64% for 0.10, 0.15, and 0.20 mg/kg remimazolam, respectively).[45] In our trial, a low dose of remimazolam (0.3 mg/kg) was used with only one single intravenous injection. Our initial experimental investigation showed that the sedative effects of remimazolam at a dose of 0.2 mg/kg were insufficient, whereas the awakening time was prolonged when administered at a dose of 0.4 mg/kg. Thus, a dose of 0.3 mg/kg remimazolam was utilized for the current trial. As per the propofol insert, the recommended dose for adult induction is 1.5–2.5 mg/kg. According to our clinical experience, a dose of 2 mg/kg is sufficient to achieve an appropriate level of sedation. Although the recommended dose of esketamine is 0.5 mg/kg, our previous experience with esketamine suggested that a dose of 0.5 mg/kg can result in prolonged awakening time for patients, and a dose of 0.3 mg/kg was found to be sufficient for providing adequate sedation and analgesic effects. The relatively low doses of experimental drugs used in our trial might explain the relatively low success rate. However, all of our surgeries were completed successfully with additional doses if necessary. In future studies, higher doses of remimazolam might be used to achieve a higher sedation success rate.

Patients in our trial who received remimazolam had higher HRs than those who received propofol, which is consistent with previous trials.[34,35,43,44,46] However, previous trials have yielded controversial results regarding the anesthesia induction time and recovery time of remimazolam. Some reported longer induction time,[39,40,46] whereas others found it shorter in remimazolam.[20] Some reported a shorter recovery time in remimazolam,[20,39,40,43] whereas some reported a longer time[44] and some reported no difference between remimazolam and propofol.[34,46] The induction time in R + E was 5 s shorter than that in P + E in our trial, whereas recover time in R + E was 1 min longer. It is necessary to have a better understanding of the rare instances of prolonged sedation when administrated with remimazolam.[16] Although statistically significant, the differences may not significantly affect the clinical procedures. Both remimazolam and propofol can provide the necessary depth and duration of anesthesia for surgical abortion procedure. Co-administration of esketamine with propofol can enable patients to achieve the goal of sedation and analgesia, while reducing the dosage of propofol and reduced the propofol-induced injection pain. With shorter duration of action, more rapid metabolism, and lower risk of serious adverse events, such as hypotension and respiratory depression, compared to propofol, co-administration of esketamine with remimazolam could be an alternative for routine outpatient procedures, such as surgical abortion, which normally takes a few minutes in a group of relatively healthy young women.

Previous trials have consistently demonstrated that remimazolam has a better safety profile than propofol, including less bradycardia treatment requirement, a lower incidence of hypotension, and less injection pain.[18,19,34,35,39,40,43,44,46] However, propofol was less likely to develop postoperative nausea and vomiting (PONV).[19,46] Our trial corroborated these findings, with no incidence of bradycardia and hypotension recorded in the R + E group, less injection site pain, and a significantly higher incidence of PONV compared to the P + E group. In addition to PONV, some patients in the R + E group, but none of those in the P + E group, in our trial, experienced hiccups during the sedation, which was consistent with the only study that reported so.[43] The precise mechanism of PONV and hiccups during sedation requires further investigation through additional clinical studies. Such studies would also shed more light on remimazolam's i.v. anesthetic properties.

Almost all clinical trials excluded participants with a history of rash to food or general anesthetic drugs. Only three clinical case reports of anaphylaxis potentially caused by remimazolam have been published,[47–49] and these cases were resolved through continuous i.v. infusion of remimazolam at full therapeutic doses. The

mechanism for remimazolam-induced anaphylaxis is not yet known due to its infrequent use. It might be due to cross-reactivity with midazolam,[48] or the additive dextran 40 in remimazolam.[49] Nonetheless, remimazolam-associated anaphylaxis is predicted to be rare.[47] Rash was the main adverse event observed in the R + E group in our trial. All were mild (only chest rash) and resolved with 10 mg Dexamethasone injection. Our trial is the first to provide evidence that a single i.v. injection of low-dose remimazolam for surgical abortion with general anesthetic is unlikely to cause severe allergic reactions. It is necessary to conduct in-depth research on the rash profile of remimazolam.

The study had several limitations. First, the predetermined dose of each sedative agent may not be optimal. Future studies investigating the efficacy and safety of different doses are necessary. Second, the anesthesia status of patients was only assessed using the MOAA/S score. Additional evaluation methods, such as the Bispectral Index, should be considered to confirm the findings. Third, the exclusion of ASA III or above patients in our study limits the generalizability of our findings, which was based on a relatively healthy population, to a more vulnerable patient population. Last but not least, as this was the first clinical trial to examine combination of esketamine with remimazolam and propofol in patients undergoing surgical abortion, no prior research is available for comparison. To validate the results, multicenter trials with larger sample sizes are required.

In summary, remimazolam is becoming more widely used in clinical practice and has the potential to alter standard operating protocols for procedural sedation due to its efficacy and safety profile. Routine procedures can be completed quickly with low risk of deep or prolonged sedation. Our trial indicates that low dose of remimazolam in combination with esketamine was featured with rapid onset and recovery, mild hemodynamic side effects, and minimal adverse events. It might be used as an alternative for surgical abortion with general anesthetic.

AUTHOR CONTRIBUTIONS

L.Y., X.M., J.C., and Y.L. wrote the manuscript. L.Y., X.M., and N.L. designed the research. L.Y., X.M., N.L., J.W., and Z.W. performed the research. J.C. and Y.L. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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