# Comparison of remimazolam besylate to propofol on induction of monitored anesthesia care on patients undergoing hysteroscopy: a multicentered, randomized, double-blind, non-inferiority study

**Si-xun Li**
Affiliated Hospital of North Sichuan Medical College
**Cheng-long Fan**
Nanchong Center Hospital
**Guang-rong Cui**
Langzhong People's Hospital
**Jing-yan Lin** ( linjingyan@nsmc.edu.cn )
Affiliated Hospital of North Sichuan Medical College

**Article**

**Keywords:**

**Posted Date:** October 4th, 2023

**DOI:** https://doi.org/10.21203/rs.3.rs-3348955/v1



**Additional Declarations:** No competing interests reported.

# Abstract

Remimazolam besylate is an intravenous benzodiazepine sedative created from “soft” drugs. The purpose of this study is to evaluate whether the effectiveness of remimazolam is non-inferior to propofol in induction of monitored anesthesia care on patients undergoing BIS-guided hysteroscopy.

This non-infertility study included patients aged 18 ~ 65 years with American Society of Anesthesiologists physical status I or II undergoing hysteroscopy. The 152 patients were prospectively recruited and randomized 1:1 to remimazolam and propofol groups.The results identified that the onset time of remimazolam was non-inferior to propofol. Compared with patients in Group P, MAP was significantly decreased at T1 ($P < 0.05$), HR was significantly increased from T3 to T5 ($P < 0.05$), and CO increased with significant difference at T8 in Group R ($P < 0.05$). Incidence of total adverse events in Group R was lower than that in Group P ($P < 0.01$). Compared with Group P, patients in Group R had a significantly longer awakening time and length of PACU stay ($P < 0.05$).

As the induction time of monitored anesthesia care on patients undergoing hysteroscopy is considered, remimazolam besylate is non-inferior to propofol. Remimazolam has less inhibition on intraoperative hemodynamics and cardiac output than propofol. Our study shows the effectiveness and safety of remimazolam besylate on patients undergoing BIS-guided hysteroscopy.


# 1. INTRODUCTION

One of the most popular treatments for individuals with cervical or endometrial diseases is hysteroscopy[1], but it comes with the physiological and psychological excruciating anguish of curettage[2–4]. The use of monitored anesthesia care (MAC) in hysteroscopy is increasing in frequency as a result of patients' growing demands for comfortable medical care[5–7]. The combination of propofol and opioids is the most popular anesthesia protocol clinically. Propofol has strong sedative effect and remarkable short half-life[8], but it may cause unpleasant advance effects included injection pain, severe respiratory depression, significant hemodynamic effects[9–11] and propofol infusion syndrome[13]. The aging population is rapidly increasing worldwide with gynecological diseases[12], a hysteroscopic sedative with adequate sedative efficacy and lower adverse effects is still required.

Remimazolam besylate is an intravenous benzodiazepine sedative created from “soft” drugs[14]. It has the characteristics of rapid onset and short half-life with no accumulation. Besides, it is independent of liver and kidney metabolism with inactive metabolites[15, 16]. It has less influence on hemodynamic and respiration than propofol without severe adverse effect[17], and can be specifically antagonized by flumazenil[18]. Currently, it has been used in general anesthesia, but the efficacy and safety of application in induction of MAC for BIS-guided hysteroscopy are undefined.

The purpose of this study is to evaluate whether the effectiveness of remimazolam is non-inferior to propofol in induction of MAC on patients undergoing BIS-guided hysteroscopy.

# 2. RESULTS

When designing this multicentered prospective trial, we planned to enroll 8 centers as we registered. However, as the inhibition of instruments and pandemic, there were only 3 centers finished this trial.

Flow diagram of the study was presented in Fig. 1: A total of 807 patients who underwent hysteroscopy between October 2021 and September 2022 assessed for eligibility in our study. Among them, 249 patients did not meet the inclusion criteria. During the study period, 558 surgeries were eligible to participate. Of these, 406 patients were excluded because of the following reasons: declined to participate (n = 198), participating in another study or already participated (n = 158), surgery cancelled (n = 50). Of the 154 patients were randomly 1:1 divided into two groups: the propofol group (Group P, n = 77) and the remimazolam group (Group R, n = 77). Of these, 7 patients were withdrawn because of the following reasons: locomotor responses occurred 3 times in Group P (n = 3) and in Group R (n = 3), failure of sedative infused (n = 1). Finally, 74 patients in Group P and 73 patients in Group R were analyzed.

# 2.1 Patient Demographic Characteristics and Perioperative Data

The patients' demographic characteristics and perioperative data were described in Table 1. Age, height, weight, body mass index (BMI) and ASA were statistically similar between the two groups ($P > 0.05$). There were no significant differences in analgesic induction doses (110 ± 13.1 mg vs 113 ± 15.4 mg), anesthesia duration (21 (10–64) min vs 19 (10–85) min) and operative duration (18 (7–57) min vs 15 (4–75) min) between the two groups ($P > 0.05$). The sedative induction dose was 12 (9–25) mg in Group R and 110 (85–142) mg in Group P. The sedation maintenance dose was 27 (11–87) mg in Group R and 120 (50–628) mg in Group P.

Table 1
Demographic Characteristics and Perioperative Data

| Variable | Group R (n = 73) | Group P (n = 74) | *P*-Value |
|---|---|---|---|
| Age (years) | 41.2 ± 8.4 | 38.7 ± 9.0 | 0.059 |
| Weight (kg) | 55.7 ± 6.3 | 56.5 ± 7.6 | 0.621 |
| Height (cm) | 158.3 ± 4.6 | 158.4 ± 5.5 | 0.837 |
| BMI ($kg/m^2$) | 22.2 ± 2.2 | 22.5 ± 2.9 | 0.638 |
| ASA / (n) | 29/44 | 34/40 | 0.083 |
| Sedative induction doses (mg) | 12 (9–25) | 110 (85–142) | |
| Sedation maintenance doses (mg) | 27 (11–87) | 120 (5-628) | |
| Analgesic induction doses (mg) | 110 ± 13.1 | 113 ± 15.4 | 0.636 |
| Anesthesia duration (min) | 21 (10–64) | 19 (10–85) | 0.403 |
| Operative duration (min) | 18 (7–57) | 15 (4–75) | 0.380 |
| Primary outcome | | | |
| Sedative onset time (s) | 74.7 ± 16.5 | 72.1 ± 16.2 | 0.331 |
| Efficacy outcomes | | | |
| Sedation success rate (%) | 96.1 (73/76) | 97.4 (74/76) | 0.649 |
| Awakening and awareness | 0 | 0 | |
| Locomotor responses (%) | 34.2 (25/73) | 37.8 (28/74) | 0.650 |
| Sedation remedial doses (mg) | 0 (0–20) | 0 (0-100) | |
| Number of sedative remedies | 0 (0–2) | 0 (0–3) | 0.898 |
| Awakening outcomes | | | |
| Length to PACU (min) | 10 (5–30) | 10 (5–30)[a] | 0.008 |
| Awakening time (s) | 520 (40-1800) | 310 (32-1076)[a] | < 0.001 |
| Satisfaction | | | |
| Patient satisfaction (score) | 10 (6–10) | 10 (6–10) | 0.159 |
| Surgeon satisfaction (score) | 10 (8–10) | 10 (8–10) | 0.173 |
| Values are presented as mean ± standard deviation or median (range) | | | |
| [a]The difference was significant at 0.05 level | | | |

## 2.2 Primary outcome

The sedative onset time was 72.1 ± 16.2s, 95% confidence interval (CI): 68.32–75.81s in the Group P. The sedative onset time of Group R was 74.7 ± 16.5s, 95% CI: 70.84–78.56s. The difference in sedative onset time between the two groups was 2.6s, 95% CI: -7.96–2.70s. As then on inferiority margin of 10s was assumed, Group R was considered non-inferior to Group P in the induction of MAC for BIS-guided hysteroscopy. The lower limit of the 95% CI for the difference in the sedative onset time was not greater than the non-inferiority limit of 10s in Fig. 2.

## 2.3 Efficacy Outcomes

There was no difference in incidence of intraoperative awakening and awareness (0 vs 0), the successful completion rate (96.1% (73/76) vs 97.4% (74/76)), locomotor responses(34.2% (25/73) vs 37.8% (28/74)), number of sedative remedies (0 (0–2) vs 0 (0–3)) between the two groups ($P > 0.05$, Table 1). BIS values of both groups were within the normal fluctuation range.

## 2.4 Awakening outcomes

Compared with Group P, patients in Group R had a significantly longer awakening time (520 (40-1800) s vs 310 (32-1076) s) ($P < 0.001$) and length of PACU stay (10 (5–30) min vs 10 (5–30) min) ($P = 0.008$, Table 1).

## 2.5 Satisfaction

There was no difference in patient satisfaction (10 (6–10) vs 10 (6–10)) and surgeon satisfaction (10 (8–10) vs 10 (8–10)) between the two groups ($P > 0.05$, Table 1).

## 2.6 Safety outcomes

Compared with patients in Group P, MAP was significantly decreased at T1 ($P < 0.05$), while HR was significantly increased from T3 to T5 in Group R ($P < 0.05$). There was no significant difference in $SpO_2$ between the two groups at T1 to T9 ($P > 0.05$, Fig. 3).

## 2.7 Adverse events outcomes

Compared with Group P (19.8%), total incidence of adverse events rate in Group R (8.1%) was lower ($P < 0.001$), with no severe adverse events or deaths occurred in the two groups. The incidence of injection pain in Group R was much lower than that in Group P (2.4% vs 28.4%, $P < 0.001$). Similarly, the incidence of hypotension (27.4% vs 62.2%) in Group R was lower than that in Group P ($P < 0.001$). There were no significant differences in respiratory depression (15.1% vs 21.6%), Bradycardia (8.1% vs 4.1%), arrhythmia (1.4% vs 2.7%), PONV (5.5% vs 4.1%) and hiccup (1.4% vs 1.4%) between the two groups (Table 2).

Table 2
The incidence of adverse events

| Adverse events | Group P (n = 74) | Group R (n = 73) | *P*-Value |
|---|---|---|---|
| Injection pain | 21 (28.4%) | 2 (2.7%)[a] | < 0.001 |
| Respiratory depression | 16 (21.6%) | 11 (15.1%) | 0.312 |
| Bradycardia | 6 (8.1%) | 3 (4.1%) | 0.494 |
| Hypotension | 46 (62.2%) | 20 (27.4%)[a] | < 0.001 |
| ECG abnormalities | 2 (2.7%) | 1 (1.4%) | 0.568 |
| PONV | 3 (4.1%) | 4 (5.5%) | 0.685 |
| Hiccup | 1 (1.4%) | 1 (1.4%) | 0.992 |
| Total incidence of adverse events | 101 (19.8%) | 42 (8.1%)[a] | < 0.001 |
| Values are presented as mean ± standard deviation or median (range) | | | |
| [a]The difference was significant at 0.05 level | | | |

## 2.8 Cardiac function outcomes

There were no significant differences in SV and LVEF between the two groups ($P > 0.05$). HR increased in Group R, while decreased in Group P, with significant difference at T1 and T2 ($P < 0.05$). Compared to Group P, CO increased in Group R with significant difference at T8 ($P < 0.05$) (**Fig, 4**).

# 3. DISCUSSION

In this study, we found that remimazolam besylate was non-inferior to propofol on induction of monitored anesthesia care on patients undergoing hysteroscopy. Patients received remimazolam intraoperatively had less variable hemodynamic impact with a lower incidence of adverse events. Besides, remimazolam had less effect on CO than propofol.

As the most commonly used analgesic in the field of anesthesia, fentanyl could cause chest wall rigidity and respiratory depression[19, 20]. In addition, the interaction and synergism between sedatives and opioids can significantly increase the incidence of respiratory depression. In the study of Lauren et al, the administration of opioids 2 minutes before remimazolam would not affect the time of arrival at loss of consciousness[21]. Sheng et al. recommended the first induction dose of remimazolam to be 0.2 mg/kg which was injected in 1 min, and then maintained at a dose of 1 mg/kg per hour[22]. So, we decided to keep the anesthesia maintained going with 1–2 mg/kg per hour remimazolam.

According to K.E et al, monitoring the depth of sedation during general anesthesia could help ensure precision anesthesia, reduce intraoperative awareness, and improve clinical outcomes[23]. Monitoring BIS

as an objective indicator of general anesthesia state of consciousness or brain function can respond to the anesthesia depth of patients to a certain extent. It was noted in the study by Andreas Eisenried et al that β Ratios may be appropriate for monitoring the depth of sedation during remimazolam administration[24], but there was no clear evidence of a device to specifically monitor for remimazolam. Another study found that the MOAA/S score was better than BIS values to assess the induction of sedation [17], but we chose BIS monitoring instead because the MOAA/S score was subjective and cannot evaluate the depth of sedation in real time to guide medication.

We observed that the onset time of the two groups was similar through BIS, and both groups could rapidly induce patients to enter the sedation stage. **Figure.3** demonstrated that BIS value induced and maintained by remimazolam was closer to 60 with more consistent and less variable compared to propofol. Matthew T.V. pointed out that deep anesthesia might increase the risk of postoperative cognitive dysfunction (POCD)[25]. Another research pointed out that reducing extreme low BIS might reduce the incidence of delirium in elderly patients[26]. The risk was further increased by the use of propofol as the global population ages. It had been recommended to target BIS value < 60 in order to avoid inadequate anesthesia depth with resultant intraoperative awareness, and the BIS value for remimazolam was slightly lower than 60. The incidence of locomotor responses was not statistically significant between the two groups. Similarly, according to the results of our postoperative follow-up, no intraoperative awareness occurred in the two groups. Therefore, 1–2 mg/kg per hour of remimazolam was used intraoperatively to maintain an uneventful complete hysteroscopy.

Patients received propofol experienced a significant HR drop after the completion of anesthesia induction and then gradually recovered. In contrast, HR of patients received remimazolam rose slightly during the operation. It demonstrated that remimazolam had less effect on HR than propofol. And remimazolam was therefore more indicated in patients who presented with bradycardia. After the anesthesia induction was completed, the decrease in MAP was significantly lower in patients received remimazolam than who received propofol. Meanwhile, MAP of patients received remimazolam was statistically significant higher, except at T3, throughout the procedure. The hemodynamic results were consistent with the findings of Jürgen Schüttler, et al[15]. It demonstrated remimazolam had less impact on blood pressure than propofol and could be used to reduce the incidence of intraoperative hypotension, facilitate the onset and maintenance of anesthesia. Similarly, a significant drop in oxygen saturation was observed in both groups after the completion of induction, it was different from the previous research[17]. We considered that may be associated with the falling back of the tongue without artificial airway in our study, however, there were no patient experienced severe hypoxemia.

No serious adverse events occurred during or after procedure in all patients in this study. The incidence of adverse events of remimazolam was significantly lower than that of propofol. One of the common complications of intravenous propofol is injection pain, while there were 2 cases of injection pain of intravenous remimazolam, and we considered the possibility that it was the result of a faster bolus injection and a much thinner venous vessel in the patients. Unlike other studies[27–29], we observed no difference in the incidence of respiratory depression between the two groups, but a sudden drop in

oxygen saturation occurred after intravenous induction of anesthesia as can be seen from the intraoperative oxygen saturation line charts. Therefore, we considered that a rapid intravenous bolus of remimazolam may cause respiratory depression. Moreover, the body position of hysteroscopy was lithotomy and it was easier to lead to tongue base suffix. Although there was not statistically significant in higher average oxygen saturation of remimazolam, it was undeniable that remimazolam had less effect on respiration than propofol during the intraoperative maintenance. The incidence of hypotension was lower with continuous infusion of remimazolam than with continuous infusion of propofol, remimazolam was more appropriate for anesthesia in hemodynamically unstable patients. Two of the arrhythmic cases occurred after intravenous propofol administration and manifested as premature ventricular contractions, which disappeared after administration of atropine or dopamine. There was no evidence that propofol can cause arrhythmia at present[30]. P-wave inversions occurred after intravenous remimazolam administration. It had not been reported in the literature and more cases were needed to explain these phenomena. The incidence of postoperative nausea and vomiting did not differ between the two groups. Propofol had definitive antiemetic effect[31], and it was unknown whether remimazolam had antiemetic properties. Hiccup was observed in both groups, and the cause of hiccup by remimazolam administration was not clear, probably due to excessive pressure of assisted ventilation, the gas entered the stomach. According to the report, an intravenous bolus of remimazolam at doses of 0.2 to 0.3 mg / kg might potentially trigger hiccup episodes lasting seconds to minutes. The adverse effect should be considered in patients at risk of reflux and aspiration, even if the symptoms were self-limiting[32].

Transthoracic ultrasound (TTE) was chosen to dynamically monitor the patient's cardiac function for reflecting hemodynamical effects more precisely and detailly. The assessments of SV, HR and CO were used as indicators. HR, SV and CO were all decreased significantly after the completion of induction by propofol. The hemodynamic properties of propofol were more primarily characterized by a decrease in sympathetic output with a concomitant decrease in systemic vascular resistance. The combined vasodilation, diminished baroreflex, reduced contractility of the venous and arterial systems were all contributors to the pathogenesis of lower CO[33]. Whereas CO was almost unchanged after the completion of anesthesia induction by remimazolam, the difference was more pronounced after continuous infusion of both sedatives. At the end of the procedure and after awaken of patients, CO started to increase in both groups. Although the effects of remimazolam on sympathetic outflow is still unknown, it does not significantly dilate peripheral vessels or reduce systemic vascular resistance thus maintaining the stability of CO[34]. The relatively stable hemodynamic with remimazolam may also be related to the stable CO.

At present, remimazolam had already been safely and effectively used in outpatient procedure sedation. It contributed to a more comfortable and safer experience for patients than propofol during upper gastrointestinal endoscopy[35]. Moreover, the successful completion rate of remimazolam tosilate-remifentanil was non-inferior to that of dexmedetomidine-remifentanil for outpatients undergoing fiberoptic bronchoscopy[36]. We need more evidence to demonstrate that remimazolam can be safely and effectively applied in the operating room.

There were some limitations in this study. First, because there was less evidence for the safety of remimazolam, we selected only patients with ASA grades - , and more studies were needed to discuss this in patients with ASA grades and . Second, because of the specificity of the surgical approach, the patients were all female, so the efficacy and safety for male patients were worth exploring. Then, no artificial airway such as oropharyngeal passage or laryngeal mask was used in this study, so the influence of tongue base suffix on low oxygen saturation cannot be excluded. Finally, we had not included the awakening quality as an indicator, so the awakening quality of remimazolam need more studies to explore.

As induction time of monitored anesthesia care on patients undergoing hysteroscopy is considered, remimazolam besylate is non-inferior to propofol. Remimazolam has less effect on intraoperative hemodynamic and CO than propofol with a lower incidence of adverse events. Our study shows the effectiveness and safety of remimazolam besylate on patients undergoing BIS-guided hysteroscopy.

# 4. Materials and methods

## 4.1 Ethics and registration

This study was a multicentered, randomized, double-blinded, non-inferiority study. It was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College [2021ER022-1] and was registered at http://www.chictr.org.cn (ChiCTR2100047432). All methods were performed in accordance with the relevant CONSORT guidelines and relevant regulations. Before beginning any procedures outlined in the protocol, written informed consent was obtained from each patient. Patients were recruited from 3 centers in China between September 2021 and September 2022 included Affiliated Hospital of North Sichuan Medical College, Nanchong Central Hospital and Langzhong People's Hospital.

## 4.2 Patient inclusion and exclusion criteria

Inclusion criteria were patients aged 18–65 years old, with American Society of Anesthesiologists (ASA) physical status or , scheduled for hysteroscopy between September 2021 and September 2022.

Exclusion criteria were patients with cardiovascular disease (ejection fraction < 40%, atrioventricular conductance disturbance, hypertension, coronary heart disease or cerebrovascular disease), liver dysfunction (transaminases above the normal level), renal failure (creatine > 150 μmol/L), preoperative opioids use, neurological disorder, diabetes, body mass index > 30 $kg/m^2$, history of neuromuscular disease, history of chronic pain, drugs or alcohol abuse.

## 4.3 Randomization and blinding

Simple randomization in a 1:1 ratio was used. Computer generated randomized numbers were concealed in identical opaque sealed envelopes distributed to three centers and stored in locked rooms. An anesthesiologist, not involved in the study design or management of the patients, opened the appropriate numbered envelope and prepared the study medications. The study drugs were kept in a bag with only

study number. Patients and the healthcare professionals involved in patient care were thus fully blinded until the study was completed.

# 4.4 Anesthesia management

All patients were routinely fasted before hysteroscopy. No premedication was administered. On arrival in the operating room, the patients were monitored with the electrocardiogram (ECG), mean arterial pressure (MAP), percutaneous oxygen saturation ($SpO_2$), heart rate (HR) and bispectralindex (BIS). An intravenous channel was established, compound sodium chloride injection was infused to maintain blood volume. All patients were allowed to breathe spontaneously with oxygen 5 L/min via face mask. Both groups received an intravenous injection of fentanil 2μg/kg for analgesic preconditioning 5 minutes before hysteroscopy and an intravenous sedative 3 minutes before hysteroscopy.

Patients in the propofol group (Group P) received 2 mg/kg propofol intravenously, with propofol maintained at a rate of 6–10 mg/kg per hour. Patients in the remimazolam (Group R) received 0.2 mg/kg remimazolam intravenously, with remimazolam administered at a rate of 1–2 mg/kg per hour.

Sedative pump rate was adjusted to maintain BIS between 40–60 intraoperatively. Additional propofol was given at a rate of 0.05 mg/kg in Group P or remimazolam was delivered at a rate of 0.1 mg/kg in Group R if BIS value > 60. A 0.5 μg/kg bolus dose of fentanyl was administered if the locomotor responses occurred with a BIS value in the recommended range contemporarily. It was identified as a sedation failure if the locomotor responses continued after 3 further doses, and propofol was used as a remedial medicine. Sedative was stopped on pump when the surgeon announced the end of the procedure.

When $SpO_2$ < 95% were observed, patients were managed by jaw thrust, with $SpO_2$ < 90% by assisted ventilation. At the same time, ephedrine or atropine was administered if hypotension (MAP < 60 mmHg) or bradycardia (HR < 60 bmp) was observed.

# 4.5 Cardiac sonography

The M-mode sampling line was placed perpendicular to the interventricular septum and the left ventricle at the level of the papillary muscle after the probe placed in the left chest and obtained a satisfactory parasternal left ventricular short axis (papillary muscle level) two-dimensional image. HR, stroke volume (SV), cardiac output (CO) were measured repetitively three times and averaged.

# 4.6 Outcomes

# 4.6.1 Primary outcome

The primary outcome of this study was the onset time which was defined as from administration to BIS value < 60.

# 4.6.2 Secondary outcomes

Efficacy outcomes included locomotor responses, sedation success rate, BIS, intraoperative awakening and awareness. We recorded the incidence of various adverse events, such as injection pain, bradycardia (HR < 60 beats/min), hypotension (MAP decreased by more than 20% of basal blood pressure), respiratory depression ($SpO_2$ < 90%), postoperative nausea and vomiting (PONV), arrhythmia, hiccup, other adverse events.

Safety outcomes included intraoperative MAP, HR, $SpO_2$, and time metrics were as follows: before anesthesia induction (T0), after successful anesthesia induction (T1), 3 min after successful anesthesia induction (T2), 6 min after successful anesthesia induction (T3), 9 min after successful anesthesia induction (T4), 12 min after successful anesthesia induction (T5), 15 min after successful anesthesia induction (T6), 18 min after successful anesthesia induction (T7), end of surgery (T8), the patient awoke (T9).

The changes of HR, SV and CO were recorded at $T_0$, $T_1$, $T_8$ and $T_9$. Visual analogue scale (VAS) was used to evaluate the satisfaction of patients and surgeons. Awakening outcomes included awakening time (from end of the surgery to patients told their birthday) and length of post-anesthesia care unit (PACU) (aldrete score reached 9) stay.

## 4.7 Sample size and statistical analysis

The sample size calculation was based on the results from previous literature. Assuming that sedative onset time of propofol and remimazolam were all about 60s. The predefined non-inferiority margin was an absolute difference of 15% between groups for the primary endpoint. With a non-inferiority margin of 20% on the relative scale, a power of 80%, a one-sided alpha of 2.5%, and assuming a dropout rate of 10%, the total sample size needed was 154 and a minimum of 77 patients were recruited for each group.

Data were statistically analyzed using statistical software SPSS 24.0. The distribution and homogeneity of the data were checked using the Shapiro-Wilk and Levene tests. Continuous outcomes were presented as means ± standard deviations (SDs) or medians and ranges, and analyzed with the Student's t-test or Kolmogorov-Smirnov Z-test as appropriate in terms of data distribution. Repeated-measures analysis of variance was used with respect to hemodynamic measurements between the two groups. Qualitative data are presented as numbers and frequencies. Between groups comparisons of qualitative variables were analyzed using $X^2$ of Fisher's exact tests. *P* values of < 0.05 were considered statistically significant.

# Declarations

### Statement of Ethics

This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College [2021ER022-1] and was registered in 18/06/2021 at http://www.chictr.org.cn (ChiCTR2100047432). A**ll methods were performed in accordance with the relevant** CONSORT **guidelines and relevant regulations**.

Before beginning any procedures outlined in the protocol, written informed consent was obtained from each patient.


### Funding

None

### Acknowledgement

None.


### Author Contributions

LJY were resposible for conceived, designed this study and collected the data. FCL were responsible for study execution. CGR was responsible for data analysis. LSX were responsible interpretation of results and manuscript writing. All authors have read and approved the final version of the manuscript.

### Data Availability Statement

Data is not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author.

### Competing Interests

The authors declare no competing interests.

## References


1. Sutton C: Hysteroscopic surgery. *J. Best Pract Res Clin Obstet Gynaecol*. **20**, 105-137(2006).
2. Gupta JK, Clark TJ, More S, Pattison H. Patient anxiety and experiences associated with an outpatient "one-stop" "see and treat" hysteroscopy clinic. *J. Surg Endosc*. **7**, 1099-1104(2004).
3. Kokanali MK, Cavkaytar S, Guzel AI, Topcu HO, Eroglu E, et al. Impact of preprocedural anxiety levels on pain perception in patients undergoing office hysteroscopy. *J. J Chin Med Assoc*. **9**, 477-481(2014).
4. Gambadauro P, Navaratnarajah R, Carli V. Anxiety at outpatient hysteroscopy. *J. Gynecol Surg*. **3**, 189-196(2015).
5. Vitale SG, Caruso S, Ciebiera M, Torok P, Tesarik J, et al. Management of anxiety and pain perception in women undergoing office hysteroscopy: a systematic review. *J. Arch Gynecol Obstet* **4**, 885-894(2020).
6. Buzzaccarini G, Alonso Pacheco L, Vitagliano A, Haimovich S, Chiantera V, et al. Pain Management during Office Hysteroscopy: An Evidence-Based Approach. *J. Medicina (Kaunas).* **58**(2022).

7. De Silva PM, Mahmud A, Smith PP, Clark TJ. Analgesia for Office Hysteroscopy: A Systematic Review and Meta-analysis. *J. J Minim Invasive Gynecol.* **27**, 1034-1047(2020).
8. Eleveld DJ, Colin P, Absalom AR, Struys M. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *J. Br J Anaesth.* **120**, 942-959(2018).
9. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *J. Br J Anaesth.* **60**, 3-9(1988).
10. Bakhtiari E, Mousavi SH, Gharavi Fard M. Pharmacological control of pain during propofol injection: a systematic review and meta-analysis. *J. Expert Rev Clin Pharmacol*. **14**, 889-899(2021).
11. Sternlo JE, Sandin RH. Recurrent respiratory depression after total intravenous anesthesia with propofol and alfentanil. *J. Anesthesia.* **53**, 378-381(1998).
12. You AH, Kim JY, Kim DH, Suh J, Han DW. Effect of remifentanil and midazolam on ED95 of propofol for loss of consciousness in elderly patients: A randomized, clinical trial. *J. Medicine (Baltimore)*. **98**(2019).
13. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *J. Br J Anaesth.* **122**, 448-459(2019).
14. Goudra BG, Singh PM. Remimazolam: The future of its sedative potential. *J. Saudi J Anaesth*. **8**, 388-391(2014).
15. Schuttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, et al. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers: Part I. Pharmacokinetics and Clinical Pharmacodynamics. *J. Anesthesiology*. **132**, 636-651(2020).
16. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, et al. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J. J Anesth*. **34**, 543-553(2020).
17. Zhang X, Li S, Liu J. Efficacy and safety of remimazolam besylate versus propofol during hysteroscopy: single-centre randomized controlled trial. *J. BMC Anesthesiol*. **21**, 156(2021).
18. Chen X, Sang N, Song K, Zhong W, Wang H, et al. Psychomotor Recovery Following Remimazolam-induced Sedation and the Effectiveness of Flumazenil as an Antidote. *J. Clin Ther.* **42**, 614-624(2020).
19. Coruh B, Tonelli MR, Park DR. Fentanyl-induced chest wall rigidity. *J. Chest.* **143**, 1145-1146(2013).
20. Boom M, Niesters M, Sarton E, Aarts L, Smith TW, et al. Non-analgesic effects of opioids: opioid-induced respiratory depression. *J. Curr Pharm Des*. **18**, 5994-6004(2012).
21. Lohmer LL, Schippers F, Petersen KU, Stoehr T, Schmith VD. Time-to-Event Modeling for Remimazolam for the Indication of Induction and Maintenance of General Anesthesia. *J. J Clin Pharmacol*. **60**, 505-514(2020).
22. Sheng XY, Liang Y, Yang XY, Li LE, Ye X, et al. Safety, pharmacokinetic and pharmacodynamic properties of single ascending dose and continuous infusion of remimazolam besylate in healthy

Chinese volunteers. *J. Eur J Clin Pharmacol.* **76**, 383-391(2020).

23. Escallier KE, Nadelson MR, Zhou D, Avidan MS. Monitoring the brain: processed electroencephalogram and peri-operative outcomes. *J. Anaesthesia*. **69**, 899-910(2014).
24. Eisenried A, Schuttler J, Lerch M, Ihmsen H, Jeleazcov C. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers: Part II. Pharmacodynamics of Electroencephalogram Effects. *J. Anesthesiology.* **132**, 652-666(2020).
25. Chan MT, Cheng BC, Lee TM, Gin T, Group CT. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J. J Neurosurg Anesthesiol*. **25**, 33-42(2013).
26. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *J. Br J Anaesth*. **110**, 98-105(201).
27. Chen SH, Yuan TM, Zhang J, Bai H, Tian M, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: A multicenter, randomized, non-inferiority, phase III trial. *J. J Gastroenterol Hepatol*. 36, 474-481(2021).
28. Zhang S, Wang J, Ran R, Peng Y, Xiao Y. Efficacy and safety of remimazolam tosylate in hysteroscopy: A randomized, single-blind, parallel controlled trial. *J. J Clin Pharm Ther*. 47, 55-60(2022).
29. Guo J, Qian Y, Zhang X, Han S, Shi Q, et al. Remimazolam tosilate compared with propofol for gastrointestinal endoscopy in elderly patients: a prospective, randomized and controlled study. *J. BMC Anesthesiol.* **22**, 180(2022).
30. Liu Q, Kong AL, Chen R, Qian C, Liu SW, et al. Propofol and arrhythmias: two sides of the coin. *J. Acta Pharmacol Sin.* **32**, 817-823(2011).
31. Borgeat A, Wilder-Smith OH, Saiah M, Rifat K. Subhypnotic doses of propofol possess direct antiemetic properties. *J. Anesth Analg*. **74**, 539-541(1992).
32. Zhang Y, Dai G, Xu H, Liu Y, Liao M, et al. Safety and efficacy of remimazolam compared with propofol in induction of general anesthesia: a reply. *R. Minerva Anestesiol.* **88**, 194-195(2022).
33. Farhan M, Hoda MQ, Ullah H. Prevention of hypotension associated with the induction dose of propofol: A randomized controlled trial comparing equipotent doses of phenylephrine and ephedrine. *J. J Anaesthesiol Clin Pharmacol*. **31**, 526-530(2015).
34. Qiu Y, Gu W, Zhao M, Zhang Y, Wu J. The hemodynamic stability of remimazolam compared with propofol in patients undergoing endoscopic submucosal dissection: A randomized trial. *J. Front Med (Lausanne)*. **9**, 938-940(2022).
35. Zhu H, Su Z, Huai X, Chen C, Zhang X, et al. Efficacy and safety of remimazolam tosylate for sedation during upper gastrointestinal endoscopy: study protocol for a multicenter randomized controlled trial. *J. Trials*. **23**, 995(2022).
36. Chen X, Xin D, Xu G, Zhao J, Lv Q. The Efficacy and Safety of Remimazolam Tosilate Versus Dexmedetomidine in Outpatients Undergoing Flexible Bronchoscopy: A Prospective, Randomized, Blind, Non-Inferiority Trial. *J. Front Pharmacol.* **13**, 902065(2022).

# Figures

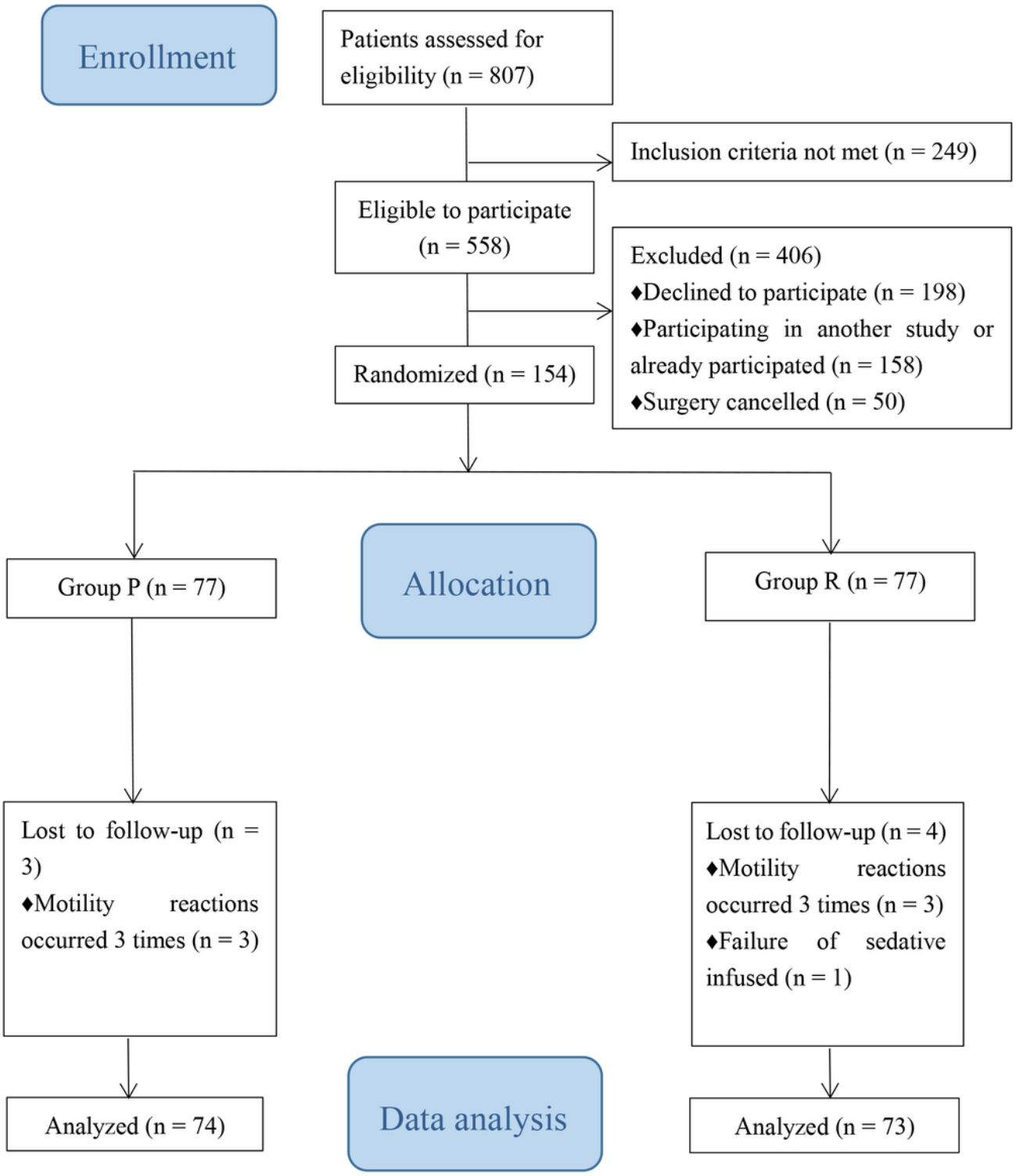
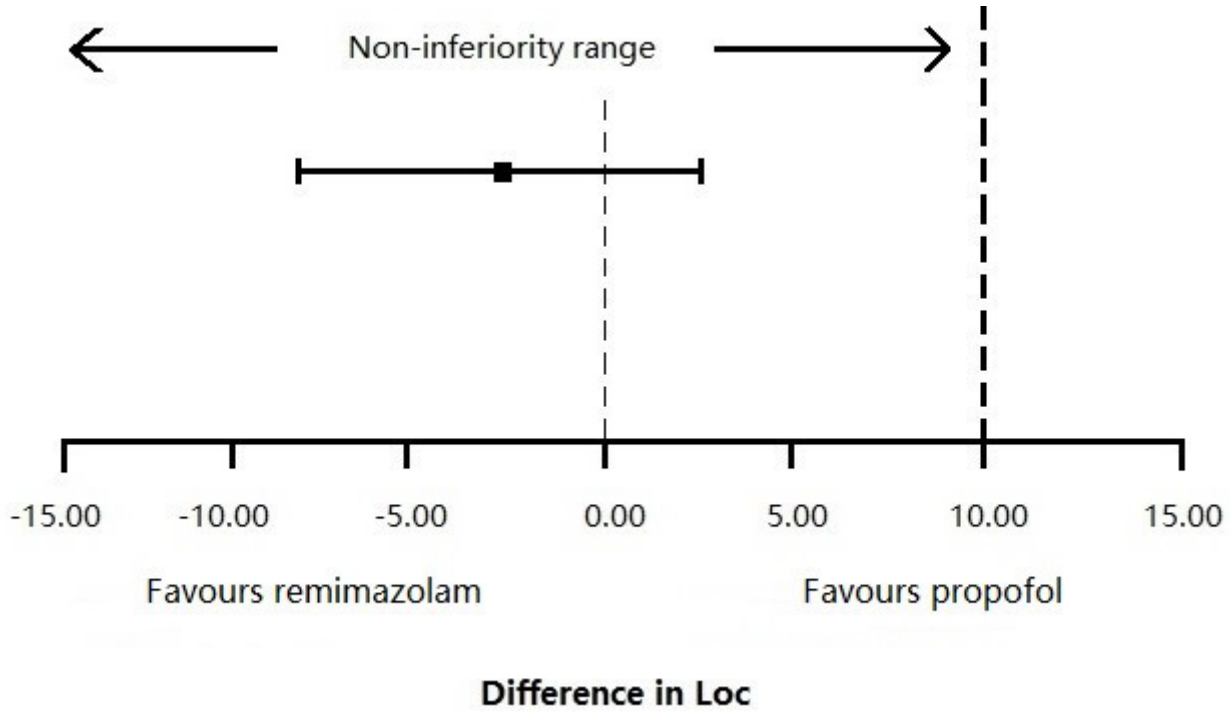


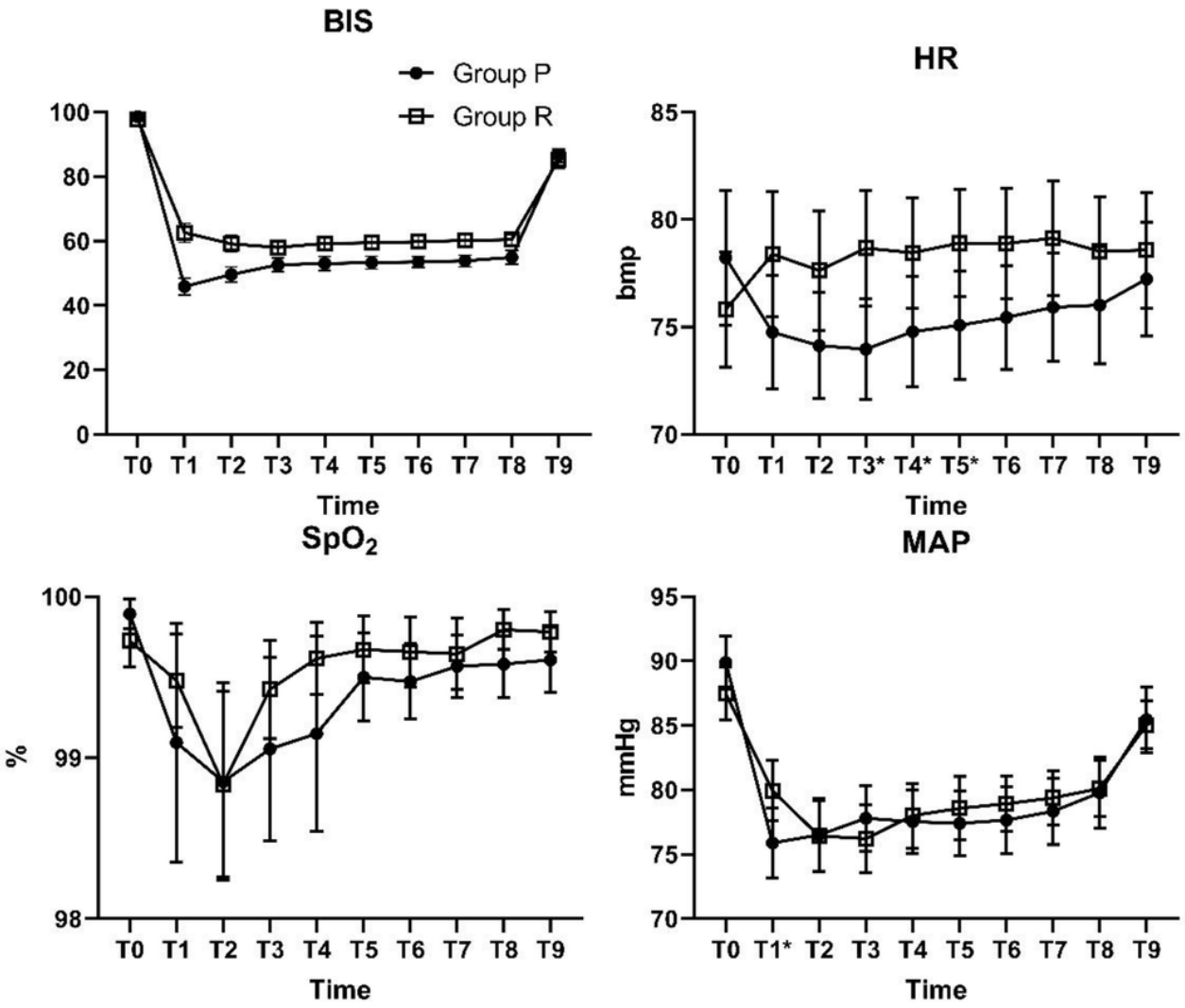

**Figure 1**

Patients flowchart with CONSORT guidelines.



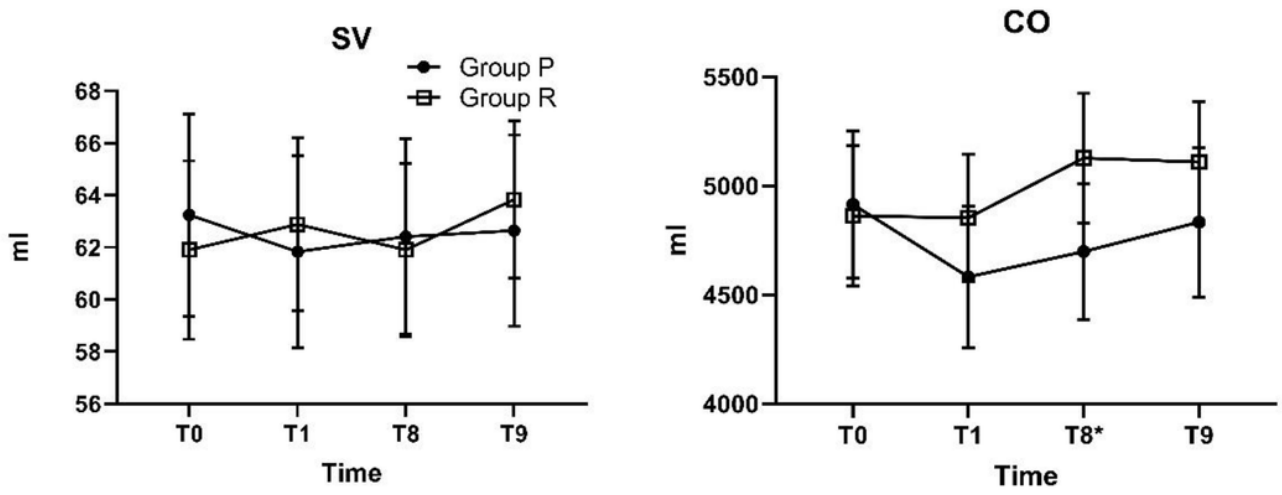

## Figure 2

Differences in the time from administration to BIS value < 60 between remimazolam and propofol. For the primary outcome of all patients, the confidence interval does not cross the non-inferiority margin, which was set at 10s, indicating that remimazolam is non-inferior to propofol.




## Figure 3

Safety outcomes and BIS. Time metrics are as follows: T0, before anesthesia induction; T1, after successful anesthesia induction; T2, 3 min after successful anesthesia induction; T3, 6 min after successful anesthesia induction; T4, 9 min after successful anesthesia induction; T5, 12 min after successful anesthesia induction; T6, 15 min after successful anesthesia induction; T7, 18 min after successful anesthesia induction; T8, end of surgery; T9, the patients awoke.




## Figure 4

Ultrasound assessment of cardiac function. Time metrics are as follows: T0, before anesthesia induction; T1, after successful anesthesia induction; T8, at the end of surgery; T9, post-awakening.