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ORIGINAL RESEARCH

Effects of Remimazolam-Propofol with Flumazenil Reversal on the Emergence Time and Hemodynamics of Patients Undergoing Laparoscopic Partial Hepatectomy: A Prospective Randomized Controlled Trial

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Background: Laparoscopic partial hepatectomy, characterized by significant surgical trauma, profound stress responses, prolonged duration, and high anesthetic requirements, may lead to delayed recovery or emergence agitation. Whether remimazolam and propofol combined with flumazenil reversal can accelerate the recovery and enhance hemodynamic stability remains controversial.

Methods: Fifty patients aged 18–70 years with American Society of Anesthesiologists (ASA) class I–III and Child-Pugh classification A or B undergoing elective laparoscopic partial hepatectomy were enrolled. Participants were randomly assigned to either the remimazolam combined with propofol group (RP group) or the propofol group (P group). Both groups received intravenous sufentanil and cisatracurium for induction, followed by either remimazolam-propofol with flumazenil reversal or propofol alone. Emergence parameters, including time to obey verbal commands, BIS over 80, and tracheal tube removal were recorded. The Sedation-Agitation Scale (SAS) and Visual Analog Scale (VAS) scores at predefined intervals, hemodynamics, and adverse events were recorded.

Results: The time to obey verbal commands ($p<0.0001$), BIS over 80 ($p=0.0011$), and tracheal tube removal ($p=0.0002$) were all significantly shorter in the RP group than in the P group. The SAS score after 30 min ($p=0.0488$) in the PACU was significantly higher, but the VAS score after 15 min ($p=0.0086$) and 30 min ($p=0.0084$) in the PACU, were significantly lower in the RP group than in the P group. MAP at T1 ($p=0.0470$) was significantly lower in the P group than in the RP group. In addition, the RP group demonstrated reduced post-induction hypotension, required no postoperative rescue analgesia, and reported no emergence agitation.

Conclusion: Compared to propofol alone, remimazolam-propofol with flumazenil reversal provides faster and more complete recovery, superior hemodynamic stability perioperatively, and reduced analgesic requirements in laparoscopic partial hepatectomy patients.

Keywords: remimazolam, propofol, flumazenil, emergence profile, hemodynamic stability, partial hepatectomy

Introduction

Laparoscopic partial hepatectomy, which is characterized by severe surgical trauma, stress reactions, long operation time and large amounts of general anesthetics, may result in delayed recovery or emergence agitation.[1] Additionally, hepatic portal occlusion is a common method to reduce blood loss during hepatectomy, which may cause ischemic-reperfusion injury to the remaining parts of the liver and large hemodynamic fluctuations.[2,3] Therefore, an ideal anesthetic protocol

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that can effectively maintain stable hemodynamics and reduce delayed recovery or emergence agitation is urgently needed.

Remimazolam, an ultrashort-acting intravenous benzodiazepine anesthetic, acts on gamma-aminobutyric acid type A ($GABA_A$) receptors to increase the influx of chloride ions, cause hyperpolarization of the nerve cell membrane, and inhibit neuronal activity, resulting in sedation and anesthesia.[4,5] Total intravenous anesthesia (TIVA) with remimazolam, which is metabolized by tissue esterases independent of liver or kidney function and characterized by a short half-life, allows for rapid reversal of effects with flumazenil.[6–8] Compared to propofol, remimazolam demonstrates a more favorable hemodynamic profile with reduced hypotension risk during anesthetic induction and maintenance in patients undergoing hip-replacement surgery or hysteroscopy.[9–11] Furthermore, remimazolam decreases the incidence of hypotension during anesthesia induction in patients undergoing laparoscopic partial hepatectomy.[12]

Propofol, a traditional intravenous anesthetic commonly used in clinical practice, is characterized by its rapid onset and short duration of action. However, it does not have a specific antagonist.[13,14] It presents several advantages, including a short stay in the recovery room, early discharge of patients, high patient satisfaction, and appropriate depth of anesthesia,[15] which may be attributed to the fact that propofol suppresses the stress response to surgery by inhibiting c-fos gene expression in the central nervous system and subsequently inhibiting the activity of the hypothalamic-pituitary-adrenal (HPA) axis.[16] Nevertheless, the elimination of propofol is mainly dependent on cardiac output and liver perfusion.[17] Prolonged and high-dose infusions of propofol during the perioperative period can lead to significant recovery delay and respiratory depression; moreover, propofol alone can cause significant injection pain.[18]

Combination of remimazolam with propofol-based TIVA provides excellent sedation with minimal adverse effects, notably low rates of hypotension, hypoxemia, respiratory depression, and injection pain, while facilitating rapid recovery and earlier discharge.[19–21] The sedative effect of remimazolam can be rapidly antagonized by flumazenil, avoiding delayed emergence in patients.[22] In addition, the antagonism of remimazolam by flumazenil may increase the incidence of nausea and vomiting within 24 hours after surgery, which can be reversed by the antiemetic effect of propofol.[23] Whether remimazolam-propofol with flumazenil reversal can maintain stable hemodynamics and reduce delayed recovery or emergence agitation in patients undergoing partial hepatectomy remains controversial. We hypothesized that remimazolam and propofol combined with flumazenil reversal can not only effectively inhibit stress reactions and maintain stable hemodynamics, but also reduce delayed recovery or emergence agitation.

Materials and Methods

Ethical Approval

The study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, Nanchong, China (approval number 2024ER328-1) and registered in the Chinese Clinical Trials Registry at http://www.chictr.org.cn (ChiCTR2400086423). The study commenced after written informed consent was obtained from all participants.

Study Population

A total of 50 patients aged 18–70 years with a BMI of 18.5–28 kg/m2 and American Society of Anesthesiologists (ASA) physical status I–III with Child-Pugh classification A or B were recruited for laparoscopic partial hepatectomy from July 2024 to February 2025 with an expected operation time of 2–5 hours. The operations were performed by the same group of tertiary physicians from the Department of Hepatologic Surgery of the Affiliated Hospital of North Sichuan Medical College.

The exclusion criteria were as follows: patients who refused to provide written informed consent; patients with uncontrolled severe hypertension; patients with significant cardiorespiratory instability, renal or adrenal insufficiency, metabolic or immune system instability, psychiatric or neurological disorders, or alcohol abuse; and patients with documented allergy or medical contraindication to the anesthetics used in the study.

Randomization and Blinding

Fifty patients were randomized into two groups: the remimazolam combined with propofol (RP) group and the propofol (P) group. Randomization was achieved via computer-generated allocations at a ratio of 1:1 in sealed opaque envelopes, with 25 patients in each group. Remimazolam (0.1 mg/kg) and propofol (0.5–1 mg/kg) were injected intravenously in the RP group, and propofol (1–2.5 mg/kg) was injected intravenously in the P group to induce anesthesia. For the maintenance of anesthesia, patients in the RP group were infused with remimazolam (0.4 mg/kg/h) and propofol (1–4 mg/kg/h), while patients in the P group were infused with propofol (4–8 mg/kg/h). Data were collected and analysed by two researchers (YXC, LJ) who were blinded to the randomization to minimise bias and achieve allocation concealment. The patient, the surgeon, and the outcome observers (JMJ), were blinded to the randomization and the group assignment.

Anesthesia Procedures

Patients in both groups routinely fasted for 8 hours and were prohibited from consuming water for 2 hours prior to surgery. No premedication was administered to the patients. After the patients were admitted to the operating room, they received mask oxygen inhalation (with a partial pressure of 100% oxygen and an oxygen flow rate of 6 L/min), intravenous access was established, and electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation (SPO_2), cerebral state index (CSI) and The patient status index (PSI) was routinely monitored. The left radial artery and the right internal jugular vein were punctured and cannulated, and the mean arterial pressure (MAP), perfusion index (PI), Heart rate (HR), pulse pressure variation (PPV), and central venous pressure (CVP) were monitored.

For anesthesia induction, remimazolam (0.1 mg/kg) and propofol (0.5–1 mg/kg) were injected intravenously for group RP, and propofol (1–2.5 mg/kg) was injected intravenously for group P. Patients in both groups received intravenous sufentanil (0.3–0.4 μg/kg) and cisatracurium (0.15 mg/kg) to facilitate tracheal intubation. Mechanical ventilation mode was administered via a mixture of oxygen in air (fraction of inspired oxygen of 0.5) and a tidal volume of 6–8 mL/kg at a rate of 12–14 breaths per minute to maintain the end-tidal carbon dioxide tension at 35–45 mm Hg.

For anesthesia maintenance, remimazolam (0.4 mg/kg/h) and propofol (1–4 mg/kg/h) were infused intravenously for group RP, and propofol (4–8 mg/kg/h) was infused for group P. Patients in both groups received an ultrasound-guided combination of rectus sheath block (RSB) and transversus abdominis plane block (TAPB) with 15 mL of 0.33% ropivacaine in each plane through a single-puncture technique and were administered remifentanil (0.1–0.2 μg/kg/min) and cisatracurium (0.1 mg/kg/h). Intravenous sufentanil 0.2 μg/kg was given every two hours to maintain CSI at 40–60 and PSI at 35–50.[24] The fluctuations in the mean arterial pressure and HR were controlled within 20% of the base value using ephedrine (3–6 mg) if necessary, and the CVP was maintained at 0–5 cmH_2O before liver resection. Oxycodone (0.1 mg/kg) was injected intravenously, and the pumping of cisatracurium was stopped at 30 min before the end of the surgery.

For emergence, remimazolam, propofol and remifentanil were stopped immediately at the end of surgery. Subsequently, intravenous flumazenil (RP group) or saline (P group) was administered in 2 mL increments, corresponding to 0.2 mg of flumazenil or 2 mL of saline, every two minutes until the recovery of consciousness. The maximum dose/volume of flumazenil/saline was 0.5 mg/5 mL. Neostigmine (0.02 mg/kg) and glycopyrronium bromide (0.005 mg/kg) were used when the patient's spontaneous respiration was restored. The tracheal tube was removed when stable spontaneous breathing was at least 5 mL/kg tidal volume, and the respiration rate was more than 7 per minute. The patient remained in the operating room until the BIS exceeded 80 and was then transferred to the post-anesthesia care unit (PACU).

Data Collection

The primary outcome was the time taken to obey verbal commands after the discontinuation of the study medications at the end of surgery. The secondary outcomes included the time taken to BIS over 80, and the time taken for tracheal tube removal after the discontinuation of the study medications. In addition, hemodynamic parameters, such as the MAP, HR, PI, and PPV, were recorded at each time point as follows: before induction of anesthesia (T0), the time of induction of anesthesia (T1), the time of endotracheal intubation (T2), the time of skin incision (T3), the time of extubation (T4), and

the time of leaving the operating room (T5). The Sedation Agitation Scale (SAS) score,[25] which ranges from failing to arouse (SAS score, 1) to dangerous agitation (SAS score, 7), and the Visual Analog Scale (VAS) score[26] (scores of 1 to 3, mild pain; scores of 4 to 6, moderate pain; and scores of 7 to 10, severe pain) were acquired upon arrival, at 15 and 30 min after arrival in the PACU. Re-sedation was defined as a decrease in the SAS score of at least 1, and emergence agitation was defined as an SAS score of 5 or more.[27,28] Once the patient appeared agitated, propofol (0.25–0.50 mg/kg) was given intravenously. Once the patient experienced moderate or severe pain, flurbiprofen (1 mg⁄kg) was administered intravenously. Other adverse events, such as post-induction hypotension, injection pain; nausea, vomiting and re-sedation within 24 hours were recorded. Peripheral venous blood samples (2 mL) were collected from the patients before the operation, 1 d after the operation, and 3 d after the operation to determine alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Statistical Analysis

The sample size was calculated using a two-sided Student's *t* test via PASS15.0 software based on the results of our preliminary study at our department. The mean time taken to obey verbal commands after the discontinuation of the study medications at the end of surgery in the RP group was 6.3 (3.6) min, and that in the P group was 10.3 (5.1) min. With an alpha error of 0.05 and a power of 90%, the required sample size was 22 per group. With respect to an anticipated dropout rate of 10%, 25 patients were required in each group.

All data are presented as the mean (standard deviation), median (25th, 75th percentile), or number of patients (%) as appropriate. Normality was evaluated via the Kolmogorov–Smirnov test. Continuous variables such as basic characteristics and emergence profiles were compared for normally distributed values using Student's *t* test, and asymmetrically distributed quantitative data were analyzed via the Mann–Whitney-U test. Comparisons of adverse events between groups were performed with the chi-square test or Fisher's exact test, as appropriate. Hemodynamic parameters, ALT and AST levels at different time points were compared by linear mixed-model analysis, and a post hoc Bonferroni correction test was performed to adjust p values for multiple comparisons. $p<0.05$ was considered statistically significant. All analyses were analyzed by SPSS 27.0 (IBM Corp., Chicago, IL, USA) and GraphPad Prism 9.5.0 (GraphPad Software, Boston, MA, USA).

Results

Fifty patients were included initially in our study, with each group consisting of 25 patients. Three, two, and two patients were excluded for intraoperative conversion to open surgery, surgery lasting more than 5 hours, and hemodynamic instability requiring blood transfusion, respectively, in the RP group. Three, three, and two patients were excluded for intraoperative conversion to open surgery, surgery lasting more than 5 hours, and hemodynamic instability requiring blood transfusion, respectively, in the P group. In total, 35 patients were recruited, 18 in the RP group and 17 in the P group. The flow chart of the patients is shown in Figure 1. There was no significant difference between the two groups in terms of the baseline characteristics, as shown in Table 1. The total infused doses of the study medications are also shown in Table 1. The total dose of remimazolam (87.2±41.3 vs 0.0±0.0 mg, $p<0.0001$) and flumazenil (0.4±0.1 vs 0.0±0.0 mg, $p<0.0001$) in the RP group were greater than in the P group, but the total dose of propofol (446.5±270.9 vs 1125.0±481.4 mg, $p<0.0001$), flurbiprofen (0.0±0.0 vs 12.6±23.7 mg, $p=0.0344$), and ephedrine (5.2±7.0 vs 8.9±4.7 mg, $p=0.0382$) in the RP group were significantly lower than in the P group. There was no difference between the RP group and P group in the dose of remifentanil (1339.0±619.1 vs 1245.0±519.0 μg, $p=0.6286$), sufentanil (48.3±8.9 vs 47.1±7.3 ug, $p=0.6477$), or cisatracurium (16.3±3.7 vs 16.4±3.1 mg, $p=0.5812$), oxycodone (6.1±0.9 vs 6.4±0.7 mg, $p=0.1570$).

Table 2 summarizes the results regarding emergence. The time taken to obey verbal command (7.8±3.4 vs 18.1±8.7 min, $p<0.0001$), BIS over 80 (5.6±3.2 vs 14.1±8.9 min, $p=0.0011$), and tracheal tube removal (11.1±3.3 vs 22.6±9.9 min, $p=0.0002$) were significantly shorter in the RP group than in the R group. The SAS score (4.0 (4.0, 4.0) vs 4.0 (3.0, 4.0), $p=0.0488$) after 30 min in the PACU was significantly higher, but the VAS score after 15 min (1.0 (0, 1.3) vs 2.0 (1.0, 3.0), $p=0.0086$) and 30 min (1.0 (0.8, 2.0) vs 2.0 (1.0, 3.0), $p=0.0084$) in the PACU were statistically lower in the RP group than in the P group. The SAS score upon arrival to the PACU (4.0 (3.0, 4.0) vs 4.0 (3.0, 4.0), $p=0.7695$), after 15 minutes in the

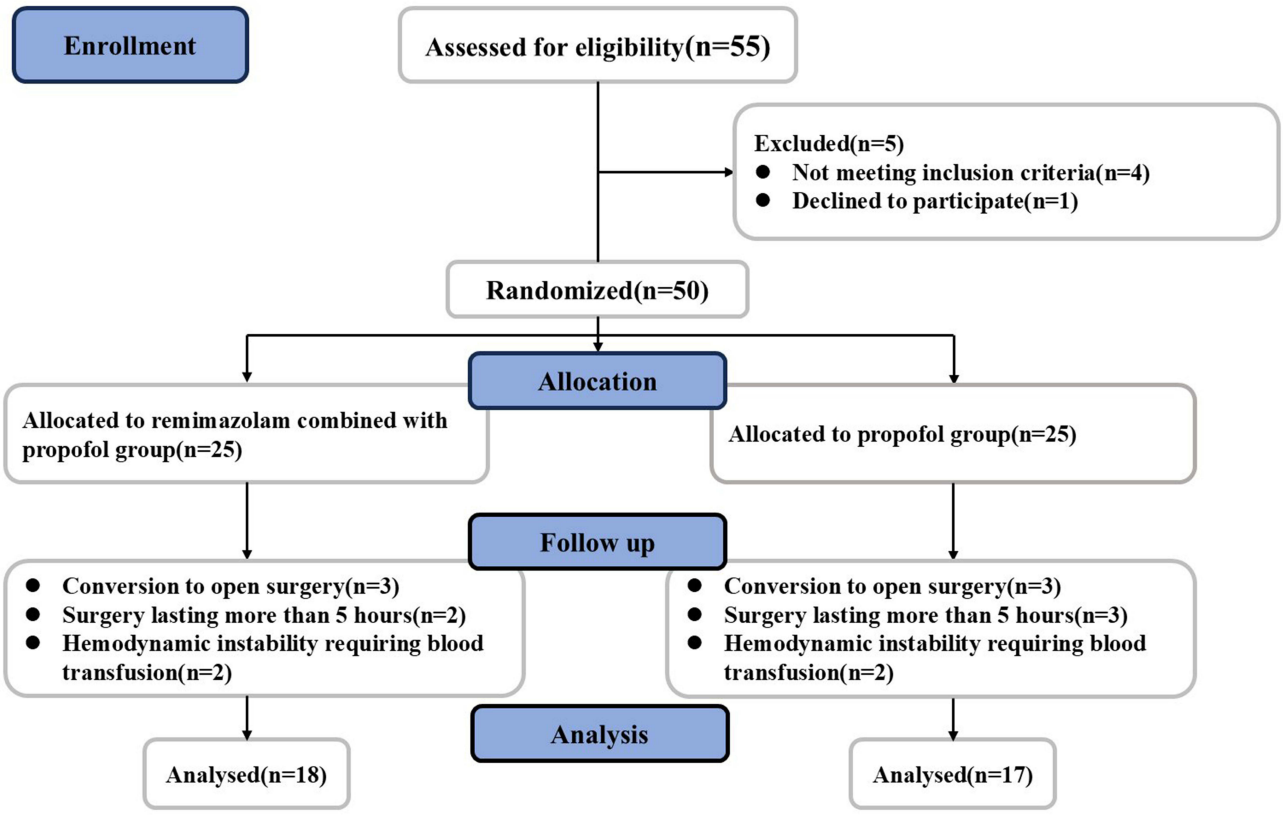

Figure 1 CONSORT flow diagram.
Abbreviation: CONSORT, Consolidated Standards of Reporting Trials.

PACU (4.0 (4.0, 4.0) vs 4.0 (3.5, 4.0), *p=0.6906*), and the VAS score (0.5 (0, 2.0) vs 2.0 (0, 3.0), *p=0.4527*) upon arrival to the PACU were comparable between the RP group and the P group.

Hemodynamic parameters at different time points in the two groups are shown in Figure 2 and Supplementary Table 1. The HR, PI and PPV values did not significantly differ between the two groups at various time points. The MAP at T1 (80.5±10.8

Table 1 Basic Characteristics, Surgical Information of the Patients and Total Infused Doses of Perioperative Drug

	Group RP (n=18)	Group P (n=17)	p-value
Sex (male/female)	10/8	8/9	0.7395
Age (years)	55.9±11.8	57.7±10.3	0.3720
BMI (kg/m^2)	22.8±2.6	23.5±2.8	0.4761
ASA status (II/III)	8/10	8/9	0.7231
Operation time (min)	176.8±69.8	165.3±60.8	0.6064
Duration of anaesthesia (min)	242.7±78.8	234.3±64.5	0.7323
Blood loss (mL)	129.4±89.9	111.8±69.7	0.6172
Urinary output (mL)	525.0±341.4	579.4±389.3	0.6626
Hepatic portal block time (min)	30.1±23.7	21.7±19.7	0.2669
Total infused doses of perioperative drug			
Remimazolam (mg)	87.2±41.3	0.0±0.0*	<0.0001
Propofol (mg)	446.5±270.9	1125.0±481.4*	<0.0001
Remifentanil (μg)	1339.0±619.1	1245.0±519.0	0.6286

(*Continued*)

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Table 1 (Continued).

	Group RP (n=18)	Group P (n=17)	p-value
Sufentanil (μg)	48.3±8.9	47.1±7.3	0.6477
Cisatracurium (mg)	16.3±3.7	16.4±3.1	0.5812
Flurbiprofen (mg)	0.0±0.0	12.6±23.7*	0.0344
Oxycodone (mg)	6.1±0.9	6.4±0.7	0.1570
Ephedrine (mg)	5.2±7.0	8.9±4.7*	0.0382
Flumazenil	0.4±0.1	0.0±0.0*	p<0.0001

Notes: Data are presented as the mean ± SD or as the number of patients, as appropriate. *$p < 0.05$ versus Group RP.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 Emergence Profiles According to Group Assignment

	Group RP (n=18)	Group P(n=17)	p-value
Emergence profile in the OR (min)			
Time taken to obey verbal commands	7.8±3.4	18.1±8.7*	<0.0001
Time taken to BIS over 80	5.6±3.2	14.1±8.9*	0.0011
Time taken to tracheal tube removal	11.1±3.3	22.6±9.9*	0.0002
SAS score in the PACU			
Upon arrival	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	0.7695
After 15 min	4.0 (4.0, 4.0)	4.0 (3.5, 4.0)	0.6906
After 30 min	4.0 (4.0, 4.0)	4.0 (3.0, 4.0)*	0.0488
VAS score in the PACU			
Upon arrival	0.5 (0.0, 2.0)	2.0 (0.0, 3.0)	0.4527
After 15 min	1.0 (0.0, 1.3)	2.0 (0.0, 3.0)*	0.0086
After 30 min	1.0 (0.8, 2.0)	2.0 (1.0, 3.0)*	0.0084

Notes: Data are presented as the mean ± SD or median (25th percentile, 75th percentile). *$p < 0.05$ versus Group RP.
Abbreviations: OR, operating room; PACU, post-anesthesia care unit; SAS, sedation agitation scale; VAS, visual analog scale.

vs 67.6±15.4 mmHg, *p=0.0470*) in group P was significantly lower than in group RP. In the RP group, the MAP at T0 (94.5 ±9.5 vs 80.5±10.8 mmHg, *p<0.0001*), T4 (98.4±9.9 vs 80.5±10.8 mmHg, *p=0.0002*), and T5 (99.6±10.2 vs 80.5±10.8 mmHg, *p=0.0002*) were significantly greater than at T1, but in the group P, the MAP at T0 (96.1±12.5 vs 67.2±16.7 mmHg, *p<0.0001*), T2 (81.3±18.2 vs 67.2±16.7 mmHg, *p=0.0003*), T4 (97.8±11.5 vs 67.2±16.7 mmHg, *p<0.0001*), and T5 (94.3 ±10.4 vs 67.2±16.7 mmHg, *p<0.0001*) were significantly greater than at T1. In the group RP, the HR at T0 (74.8±8.8 vs 86.9 ±12.0 beats/min, *p=0.0289*), T2 (74.3±13.2 vs 86.9±12.0 beats/min, *p=0.0281*), T3 (68.2±8.7 vs 86.9±12.0 beats/min, *p=0.0005*) were significantly higher than at T5, but in the P group, the HR at T0 (77.7±9.9 vs 91.2±11.7 beats/min, *p=0.0078)*, T1 (70.0±12.1 vs 91.2±11.7 beats/min, *p<0.0001*), T2 (74.4±16.4 vs 91.2±11.7 beats/min, *p<0.0001*), and T3 (63.3±9.3 vs 91.2±11.7 beats/min, *p<0.0001*) were significantly higher than at T5. The PI decreased after the operation in both groups. In the RP group, the PI at T0 (2.9±2.0 vs 1.1±0.9, *p=0.0033*; 2.9±2.0 vs1.4±1.1, *p=0.0328*), T1 (4.0±2.4 vs 1.1±0.9, *p=0.0002*; 4.0±2.4 vs 1.4±1.1, *p=0.0026*), and T2 (3.6±1.8 vs 1.1±0.9, *p=0.0013*; 3.6±1.8 vs1.4±1.1, *p=0.0121*) were significantly higher than at T4, T5, but in the P group, the PI at T0 (3.2±2.4 vs 1.4±0.9, *p=0.0413*), T1 (4.3±2.1 vs 1.4±0.9,

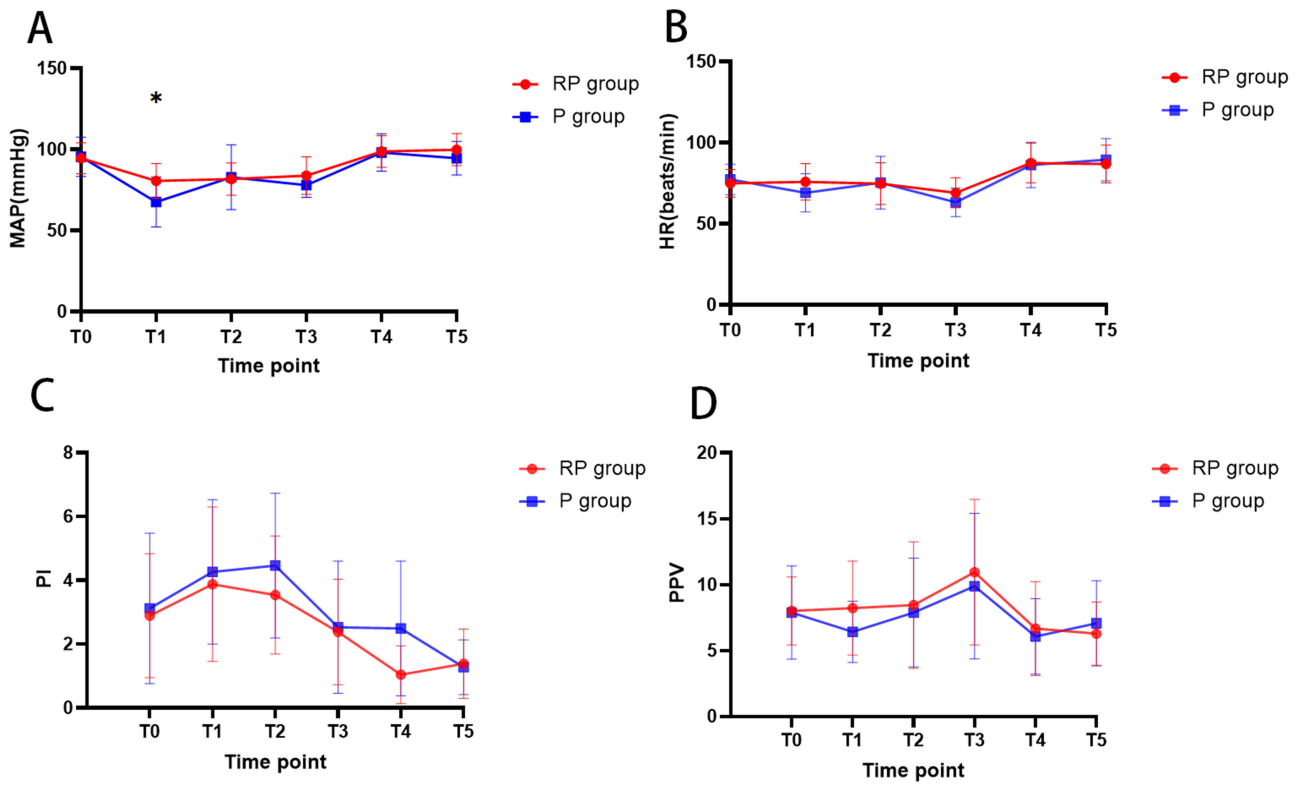

Figure 2 Hemodynamic parameters variations at different time points. Changes in MAP during perioperative period (**A**), changes in HR during perioperative period (**B**), changes in PI during perioperative period (**C**), changes in PPV during perioperative period (**D**). *$p<0.05$ versus Group RP. T0: before induction of anesthesia, T1: the time of induction of anesthesia, T2: the time of endotracheal intubation, T3: the time of skin incision, T4: the time of extubation; T5: the time of leaving the operating room.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; PI, perfusion index; PPV, pulse pressure variation.

p=0.0006), and T2 (4.7±2.2 vs 1.4±0.9, *p=0.0003*) were significantly higher than at T5. Therefore, hemodynamic fluctuations were observed in group P.

Liver function variations in both groups are shown in Table 3. There were no statistically significant differences in the ALT or AST levels in the RP group at preoperative, 1 d postoperative or 3 d postoperative time points compared with those in the P group. Additionally, the ALT levels at 1 d (339.8±194.5 vs 45.9±53.6 U/L, *p<0.0001*; 354.6±168.0 vs 36.1 ±16.9 U/L, *p<0.0001*) and 3 d (123.1±76.6 vs 45.9±53.6 U/L, *p=0.0068*; 122.4±54.7 vs 36.1±16.9 U/L, *p<0.0001*) postoperatively were significantly greater than at preoperatively in the RP and P groups. The AST levels at 1 d (340.1 ±158.0 vs 36.5±15.6 U/L, *p<0.0001*) and 3 d (76.3±58.2 vs 36.5±15.6 U/L, *p=0.0387*) postoperatively were significantly greater than those at preoperative in the P group, although the AST level at 1 d (355.8±224.8 vs 36.3±22.2 U/L, *p<0.0001*) postoperatively was significantly higher than at preoperatively, the AST level at 3d postoperatively was not affected in the RP group.

Table 3 Liver Function Indicators at Different Time Points

Indicators		Preoperative	1d postoperative	3d postoperative
ALT (U/L)	Group RP (n=18)	45.9±53.6	339.8±194.5*	123.1±76.6*#
	Group P (n=17)	36.1±16.9	354.6±168.0*	122.4±54.7*#
AST (U/L)	Group RP (n=18)	36.3±22.2	355.8±224.8*	49.9±31.9#
	Group P (n=17)	36.5±15.6	340.1±158.0*	76.3±58.2*#

Notes: Data are presented as the mean ± SD. *$p<0.05$ versus Preoperative. #$p<0.05$ versus 1d postoperative.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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Table 4 Comparison of Adverse Events Between the Groups (n, %)

	Group RP (n=18)	Group P (n=17)	*p-value*
Injection pain	4 (22.2)	8 (47.1)	0.1642
Post-induction hypotension (MBP < 65 mmHg)	3 (16.7)	14 (82.4)*	<0.0001
Postoperative nausea within 24 hours	1 (5.6)	5 (29.4)	0.0877
Postoperative vomiting within 24 hours	1(5.6)	2 (11.8)	0.6026
Emergence-related side effects			
Re-sedation with 24 hours	1 (5.6)	2 (11.8)	0.6026
Emergence agitation	0 (0.0)	0 (0.0)	1.0000
Flumazenil dose of the patients (0.2/0.4/0.5mg)	0 (0)/7 (38.9)/11 (61.1)		

Notes: Data are presented as the number (%) of patients. *$p < 0.05$ versus Group RP.
Abbreviation: MBP, mean arterial pressure.

The information regarding adverse events is presented in Table 4. The incidence of post-induction hypotension (16.7% vs 82.4%, $p<0.0001$) was significantly lower in the RP group than in the P group, and the incidence of injection pain, postoperative nausea and vomiting were comparable between the two groups. Re-sedation within 24 hours was observed in the RP group (1 (5.6%) patient) and P group (2 (11.8%) patients), and no difference was found between the two groups. Moreover, none of the patients complained of emergence agitation. The dose of flumazenil used in the operating room ranged from 0.2 to 0.5 mg, and a detailed distribution is summarized in Table 4.

Discussion

In this randomized clinical trial, compared with propofol alone, remimazolam combined with propofol-based TIVA with routine use of flumazenil resulted in a faster recovery of consciousness and more stable hemodynamics during induction of anesthesia in patients undergoing laparoscopic partial hepatectomy. In our study, a maximum dose of 0.5 mg flumazenil was used because a lower total clearance is associated with a greater risk of reappearance of the remimazolam effect after a flumazenil bolus.[29] However, re-sedation rarely occurred in some patients after arriving at the PACU in the RP or P groups. Our findings provide new insight into the efficacy and safety of flumazenil use after remimazolam combined with propofol-based TIVA for more than two hours.

At present, partial hepatectomy has become the first-line effective treatment for primary liver cancer.[30] However, due to the effects of surgical trauma and stress, most patients suffer from postoperative complications such as pain, hypotension, impaired organ function, and delayed recovery. Therefore, reasonable selection of anesthetics during the perioperative period to reduce adverse effects on emergence profiles and hemodynamics is conducive to improving patient prognosis.

Propofol is currently one of the most widely used intravenous anesthetics and is known for its rapid onset and recovery.[31] In recent years, remimazolam has raised much attention as an alternative to propofol. Nevertheless, previous studies have reported that remimazolam has a longer recovery time compared to propofol without the use of flumazenil.[11] The combination of remimazolam and low-dose propofol has been proven to provide high-quality sedation and safety.[20] Although propofol has no specific antagonist, routine use of flumazenil after a long duration of remimazolam combined with propofol-based TIVA significantly reduced the time taken to obey verbal commands, BIS over 80, and tracheal tube removal, improved emergence quality when compared with propofol alone-based TIVA in our study. Remimazolam and propofol combined with flumazenil has added a new concept to “fast tracking” recovery, which is emphasized by clinicians.

Furthermore, the VAS score after 15 min and 30 min in the PACU were statistically lower in the RP group than in the P group. Additionally, postoperative rescue analgesia was not required in the RP group. In line with previous reports, Hung et al[32] found that remimazolam was associated with a lower risk of rescue analgesia requirement in the PACU in

comparison with propofol. This may be related to the fact that remimazolam alleviates the effect of remifentanil-induced hyperalgesia which can increase the pain intensity after surgery especially at 1 h postoperatively.[32] Surprisingly, our results indicated that the incidence of re-sedation within 24 hours in the RP group (5.6%) was lower than in the P group (11.8%), but the difference was not statistically significant. This finding was inconsistent with a previous report that demonstrated the effectiveness of remimazolam-based TIVA with flumazenil reversal in reducing emergence time, but a significant incidence of re-sedation was observed in the PACU.[33] This can be explained by two aspects: first, propofol is a sedative that acts mainly on the β subunit of $GABA_A$ receptors. It directly opens chloride (Cl^-) channels. Remimazolam is a sedative that activates benzodiazepine receptors located on the α subunit of $GABA_A$ receptors. It increases the frequency of Cl^-channel opening. These two sedatives may share transmembrane binding sites on the $GABA_A$ receptor.[34–36] Second, in the present study, remimazolam (0.4 mg/kg/h) was used in combination with propofol, and the residual concentration of remimazolam at the end of surgery was not high enough to affect the reversal sedative effect after the flumazenil bolus.[29]

Considering the hemodynamic parameters, propofol alone induced hemodynamic fluctuations during the perioperative period, and the suppressive effects of HR and MAP after the induction of anesthesia were also significantly milder in patients treated with remimazolam combined with propofol than in patients treated with propofol alone. These results are consistent with those of previous studies. Patients sedated with remimazolam have stable arterial blood pressure and heart rate according to examinations[37] and laparoscopic partial hepatectomy.[12] Notably, the PI decreased after the operation, and the ALT and AST levels of patients in both groups were higher than those preoperatively and 1 d postoperatively. To our knowledge, total or partial exclusion of blood flow to the liver during resection is highly important for controlling bleeding, which may lead to hepatic ischemia and reperfusion injury and result in a decreased peripheral PI and impaired liver function.[3] Furthermore, there were no statistically significant differences in the ALT or AST levels between the two groups during preoperative and postoperative periods. The AST level recovered to baseline at 3 d postoperatively in the RP group, indicating that the combination of remimazolam and propofol may protect liver function. In addition, the investigation of adverse reactions revealed that the rates of injection pain, postoperative nausea and vomiting in the RP group were lower than those in the P group, but the differences were not statistically significant. Additional experiments are required for further confirmation.

The present study has several potential limitations. First, hemodynamic parameters such as cardiac output (CO), cardiac index (CI), stroke volume variation (SVV), and systemic vascular resistance (SVR) can be monitored to predict perioperative hypotension and reduce the risk of complications. Second, the present study is a single-center study that includes only patients with Child-Pugh classification A or B, with a relatively small sample size and short-term follow-up, a multicenter, large sample size, randomized, and double-blind trial needs to be conducted in the follow-up for further validation of the effects of remimazolam-propofol with flumazenil reversal on the emergence profiles and hemodynamics of patients undergoing laparoscopic partial hepatectomy.

Conclusion

Compared to propofol alone, remimazolam-propofol with flumazenil reversal provides faster and more complete recovery, superior hemodynamic stability perioperatively, and reduced analgesic requirements in laparoscopic partial hepatectomy patients.

Abbreviations

$GABA_A$, gamma amino butyric acid type A; TIVA, total intravenous anesthesia; HPA, hypothalamic-pituitary-adrenal; BMI, body mass index; ECG, electrocardiogram; HR, heart rate; SPO_2, pulse oxygen saturation; CSI, cerebral state index; PSI, patient status index; MAP, mean arterial pressure; PI, perfusion index; PPV, pulse pressure variation; CVP, central venous pressure; TAPB, transversus abdominis plane block; PACU, post-anesthesia care unit; SAS, sedation agitation scale; VAS, visual analog scale; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CO, cardiac output; CI, cardiac index; SVV, stroke volume variation; SVR, systemic vascular resistance.

Data Sharing Statement

The data supporting the study findings are available from the corresponding author upon request.

Ethics Approval and Informed Consent

The study was approved by the Institutional Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, China (Approved Approval No. 2024ER328-1) and was registered on the Chinese Clinical Trials Registry at http://www.chictr.org.cn (ChiCTR2400086423). All participants provided their written informed consent. We confirm our study complies with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

References

1. Cui L, Zou Y, Zhang L, et al. Effects of dexmedetomidine on the recovery quality of donors undergoing pure laparoscopic donor hepatectomy. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2024;55(3):693–698. doi:10.12182/20240560603
2. Taman HI, Elhefnawy E. Hepatic protective effect of dexmedetomidine after partial hepatectomy surgery: a prospective controlled study. *Anesth Essays Res*. 2019;13(1):132–137. doi:10.4103/aer.AER_106_18
3. Kong E, Yuan C, Li Y, et al. Protective efficiency comparison of direct and remote ischemic preconditioning on ischemia reperfusion injury of the liver in patients undergoing partial hepatectomy. *Biomed Res Int*. 2023;2023:2763320. doi:10.1155/2023/2763320
4. Sneyd JR, Rigby-Jones AE. Remimazolam for anaesthesia or sedation. *Curr Opin Anaesthesiol*. 2020;33(4):506–511. doi:10.1097/ACO.0000000000000877
5. Sneyd J. Remimazolam-current status, opportunities and challenges. *Anesthesiol Periop Sci*. 2023;1(25):1–10. doi:10.1007/s44254-023-00021-7
6. Stöhr T, Colin PJ, Ossig J, et al. Pharmacokinetic properties of remimazolam in subjects with hepatic or renal impairment. *Br J Anaesth*. 2021;127(3):415–423. doi:10.1016/j.bja.2021.05.027
7. Kilpatrick GJ. Remimazolam: non-clinical and clinical profile of a new sedative/anesthetic agent. *Front Pharmacol*. 2021;12:690875. doi:10.3389/fphar.2021.690875
8. Aya D, Hoshi T, Yamaguchi H. Predicting the amount of flumazenil needed to antagonize remimazolam. *Eur J Gastroenterol Hepatol*. 2021;33(10):1335–1336. doi:10.1097/MEG.0000000000002201
9. Doi M, Morita K, Takeda J, et al. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anesth*. 2020;34:543–553. doi:10.1007/s00540-020-02788-6
10. Zhang J, Wang X, Zhang Q, et al. Application effects of remimazolam and propofol on elderly patients undergoing Hip replacement. *BMC Anesthesiol*. 2022;22:118. doi:10.1186/s12871-022-01641-5
11. Zhang X, Li S, Liu J. Efficacy and safety of remimazolam besylate versus propofol during hysteroscopy: single-centre randomized controlled trial. *BMC Anesthesiol*. 2021;21:156. doi:10.1186/s12871-021-01373-y
12. Xing Q, Zhou X, Zhou Y, et al. Comparison of the effects of remimazolam tosylate and propofol on immune function and hemodynamics in patients undergoing laparoscopic partial hepatectomy: a randomized controlled trial. *BMC Anesthesiol*. 2024;24(1):205. doi:10.1186/s12871-024-02589-4
13. Chang Y, Huang YT, Chi KY, et al. Remimazolam versus propofol for procedural sedation: a meta-analysis of randomized controlled trials. *Peer J*. 2023;11:e15495. doi:10.7717/peerj.15495
14. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med*. 2002;30(1):119–141. doi:10.1097/00003246-200201000-00020
15. Miller TE, Gan TJ. Total intravenous anesthesia and anesthetic outcomes. *J Cardiothorac Vasc Anesth*. 2015;29(Suppl. 1):S11–5. doi:10.1053/j.jvca.2015.01.022
16. Schricker T, Lattermann R, Fiset P, et al. Integrated analysis of protein and glucose metabolism during surgery: effects of anesthesia. *J Appl Physiol*. 2001;91(91):2523–2530. doi:10.1152/jappl.2001.91.6.2523
17. Minto CF, Schnider TW. Contributions of PK/PD modeling to intravenous anesthesia. *Clin Pharmacol Ther*. 2008;84:27–38. doi:10.1038/clpt.2008.100
18. Mao Y, Guo J, Yuan J, et al. Quality of recovery after general anesthesia with remimazolam in patients' undergoing urologic surgery: a randomized controlled trial comparing remimazolam with propofol. *Drug Des Devel Ther*. 2022;16:1199–1209. doi:10.2147/DDDT.S359496
19. Wang C, Gao Y, Li J, et al. Safety and effectiveness of the combination of remimazolam tosilate and propofol in gastroscopy: a multicenter, randomized controlled, single-blind clinical trial. *Front Pharmacol*. 2023;14(14):1124667. doi:10.3389/fphar.2023.1124667

20. Zhang F, Chang H, Qing W, et al. Remimazolam tosylate combined with low-dose propofol improves sedation and safety in hysteroscopy. *Drug Des Devel Ther*. 2022;16:4101–4108. doi:10.2147/DDDT.S390403
21. Tan H, Lou AF, Wu JE, et al. Determination of the 50% and 95% effective dose of remimazolam combined with propofol for intravenous sedation during day-surgery hysteroscopy. *Drug Des Devel Ther*. 2023;17:1753–1761. doi:10.2147/DDDT.S406514
22. Chen X, Sang N, Song K, et al. Psychomotor recovery following remimazolam-induced sedation and the effectiveness of flumazenil as an antidote. *Clin Ther*. 2020;42(4):614–624. doi:10.1016/j.clinthera.2020.02.006
23. Wei Y, Zhu M, Man Y, et al. Clinical study of flumazenil antagonizing remimazolam on nausea and vomiting after gynecologic day surgery. *Drug Des Devel Ther*. 2024;18:631–638. doi:10.2147/DDDT.S444313
24. Jang YE, Kim EH, Lee JH, et al. Usefulness of bispectral index and patient state index during sevoflurane anesthesia in children: a prospective observational study. *Medicine*. 2022;101(30):e29925. doi:10.1097/MD.0000000000029925
25. Feng Y, Chen XB, Yuan WG, et al. Comparison of the level of free hexafluoro-isopropanol in adults' blood and the incidence of emergence agitation after anesthesia with different concentrations of sevoflurane in laparoscopic gastrointestinal surgery: a randomized controlled clinical trial. *Clin Ther*. 2019;41(11):2263–2272. doi:10.1016/j.clinthera.2019.08.022
26. He S, Renne A, Argandykov D, et al. Comparison of an emoji-based visual analog scale with a numeric rating scale for pain assessment. *JAMA*. 2022;328(2):208–209. doi:10.1001/jama.2022.7489
27. Lee SJ, Sung TY. Emergence agitation: current knowledge and unresolved questions. *Korean J Anesthesiol*. 2020;73:471–485. doi:10.4097/kja.20097
28. Xara D, Silva A, Mendonca J, et al. Inadequate emergence after anesthesia: emergence delirium and hypoactive emergence in the postanesthesia care unit. *J Clin Anesth*. 2013;25:439–446. doi:10.1016/j.jclinane.2013.02.011
29. Masui K. Caution!! Reappearance of remimazolam effect after a flumazenil bolus: a larger bolus of flumazenil and a lower total remimazolam clearance are higher risks. *J Anesth*. 2023;37(1):1–5. doi:10.1007/s00540-022-03107-x
30. Pan SB, Wu CL, Hou H, et al. Open hepatectomy versus laparoscopic in the treatment of primary left-sided hepatolithiasis: a propensity, long-term follow-up analysis at a single center. *Zhonghua Wai Ke Za Zhi*. 2020;58(7):530–538. doi:10.3760/cma.j.cn112139-20191114-00561
31. Bryson HM, Fulton BR, Faulds D. Propofol. An update of its use in anaesthesia and conscious sedation. *Drugs*. 1995;50:513–559. doi:10.2165/00003495-199550030-00008
32. Hung KC, Wang WT, Liu WC, et al. Comparing subjective quality of recovery between remimazolam- and propofol-based total intravenous anesthesia for surgical procedures: a meta-analysis. *Syst Rev*. 2024;13(1):235. doi:10.1186/s13643-024-02660-8
33. Oh EJ, Chung YJ, Lee JH, et al. Comparison of propofol vs. remimazolam on emergence profiles after general anesthesia: a randomized clinical trial. *J Clin Anesth*. 2023;90:111223. doi:10.1016/j.jclinane.2023.111223
34. Sajeeda S, Kumar L, Verma R. An overview of analytical methods for the estimation of propofol in pharmaceutical formulations, biological matrices, and hair marker. Crit. *Rev Anal Chem*. 2022;52(7):1694–1701. doi:10.1080/10408347.2021.1910927
35. McGoldrick MK, Galanopoulou AS. Developmental pharmacology of benzodiazepines under normal and pathological conditions. *Epileptic Disord*. 2014;16(1):S59–S68. doi:10.1684/epd.2014.0690
36. Kim JJ, Gharpure A, Teng J, et al. Shared structural mechanisms of general anaesthetics and benzodiazepines. *Nature*. 2020;585(7824):303–308. doi:10.1038/s41586-020-2654-5
37. Sneyd JR, Gambus PL, Rigby-Jones AE. Current status of perioperative hypnotics, role of benzodiazepines, and the case for remimazolam: a narrative review. *Br J Anaesth*. 2022;127(1):41–55. doi:10.1016/j.bja.2021.03.028