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CLINICAL TRIAL REPORT

Comparative Analysis of Hemodynamic Effects of Remimazolam and Propofol Combined with Esketamine in Colonoscopic Procedures in the Elderly

Bo-Ran Deng[1,*], Yang Zhang[2,*], Zi-Feng Xie[3,*], Ding-Ding Wang[4,*], Tao Zeng[1], Dong-Bo Zhang[3], Li Huang[1], Qi-Yan Wang[1], Tu Shen[3], Qiao-Ling Wu[3]

[1]Surgical Anesthesia Center, Zigong Hospital of TCM, Zigong, 643000, People's Republic of China; [2]Department of Anesthesia, Da'an District Maternal and Child Health Hospital, Zigong, 643000, People's Republic of China; [3]Department of Anesthesia, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, 121000, People's Republic of China; [4]Department of Anesthesia, EYE & ENT Hospital of Fudan University, Shanghai, 200031, People's Republic of China

*These authors contributed equally to this work

Correspondence: Tu Shen; Qiao-Ling Wu, Department of Anesthesia, the First Affiliated Hospital of Jinzhou Medical University, No. 40, Section 3, Songpo Road, Linghe District, Jinzhou, 121000, People's Republic of China, Email shentu2011@sina.com; wqiaoling2013@sina.com

Purpose: The debate continues over the differential impact of remimazolam vs propofol on hemodynamic stability. This study aims to elucidate the effects of a combination of remimazolam and esketamine vs propofol and esketamine on hemodynamic parameters in elderly patients undergoing painless colonoscopies.

Patients and Methods: We conducted a randomized controlled trial involving 754 patients, divided equally between two treatment groups. The remimazolam-esketamine group (RE group) received 0.15 mg/kg of remimazolam and 0.3 mg/kg of esketamine. Conversely, the propofol-esketamine group (PE group) was administered 1.5 mg/kg of propofol with 0.3 mg/kg of esketamine. Primary outcomes focused on the incidence of hypotension. Secondary outcomes assessed were other hemodynamic adverse events, intraoperative blood pressure and heart rate fluctuations, usage of vasoactive agents, sedation efficacy, and additional adverse reactions.

Results: Hypotension occurred significantly less frequently in the RE group (9.78%, 95% confidence interval[CI]: 6.67–12.87%) compared to the PE group (23.57%, 95% CI: 21.22–30.52%), $P<0.001$. The RE group also showed lower incidences of sinus tachycardia, sinus bradycardia, and required less support from vasoactive agents ($P<0.001$). Additionally, the RE group experienced smaller fluctuations in blood pressure and heart rate ($P<0.05$). Both groups achieved a 100% sedation success rate. Notably, the RE group had a longer induction period but a quicker recovery time ($P<0.001$), and lower rates of respiratory depression ($P=0.006$) and injection pain ($P<0.001$).

Conclusion: Remimazolam combined with esketamine offers superior hemodynamic stability and significantly reduces adverse event rates compared to propofol plus esketamine in elderly patients undergoing painless colonoscopies, while maintaining effective sedation.

Keywords: remimazolam, esketamine, colonoscopy, elderly patients, hemodynamic effects

Introduction

As gastrointestinal diseases become increasingly complex and prevalent, the importance of endoscopic examinations has grown significantly. These procedures are crucial for diagnosing, treating, and conducting early screenings of gastrointestinal disorders.[1] However, endoscopies often induce fear, nausea, vomiting, pain, and other discomforts in patients. These side effects can complicate surgical procedures, reduce patient cooperation, and worsen the overall medical experience.

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Consequently, sedation or anesthesia is commonly employed to enhance patient comfort and satisfaction. Indeed, statistics reveal that over 98% of patients opt for painless endoscopy, underscoring its acceptance and preference.[2]

The rapid pace of global aging has led to an increasing proportion of the elderly, particularly in China, where one-fifth of the world's elderly reside.[3] Elderly patients, due to their unique physiological conditions, are more susceptible to adverse events during the perioperative period, such as hemodynamic instability, hypoxia, hypothermia, and delirium. These risks pose significant challenges for anesthesiologists.

Balanced anesthesia reduces the quantity of each anesthetic required, diminishing the likelihood of adverse reactions. A classic regimen for endoscopies involves the combination of propofol with opioids, which has reportedly increased the rate of painless gastroscopies and colonoscopies by fourfold.[4] However, propofol is associated with notable drawbacks, including hemodynamic instability and significant respiratory depression that can lead to severe adverse events.[5]

Esketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with high affinity, has been shown to have a lower incidence of hemodynamic adverse events compared to opioids, according to a meta-analysis of 18 studies.[6,7] Research indicates that using esketamine in conjunction with propofol (PE) for painless gastroscopy and colonoscopy in elderly patients can reduce the amount of propofol needed without affecting the time to recover from anesthesia, while also decreasing the incidence of hypotension.[8]

Remimazolam, a novel benzodiazepine sedative, is characterized by its rapid onset and swift recovery, facilitated by its quick hydrolysis into an inactive metabolite by tissue esterases.[9] Since its introduction to the market, remimazolam has been effectively applied in procedural sedation (for both induction and maintenance), general anesthesia, and ICU sedation. For elderly patients undergoing painless gastroscopy or colonoscopy, remimazolam, when combined with opioids, offers sedative effects comparable to propofol but with a reduced risk of adverse hemodynamic events and respiratory depression.[10] A study by Li et al involving 150 patients aged 35–65 years showed that while remimazolam combined with esketamine (RE) provided more stable hemodynamics compared to the PE regimen, the incidence of adverse hemodynamic events was similar.[11] However, it remains unclear if there are significant differences in hemodynamic stability and adverse event rates between the RE and PE regimens for painless gastroscopy or colonoscopy in elderly patients.

This trial was designed to assess the impact of remimazolam combined with esketamine on hemodynamics during painless gastroscopy or colonoscopy in elderly individuals, aiming to offer a safer and more effective clinical medication regimen. Our hypothesis is that remimazolam combined with esketamine, compared to propofol combined with esketamine as a balanced anesthesia approach, will reduce the incidence of adverse hemodynamic events and provide improved hemodynamic stability in elderly patients receiving painless gastroscopy or colonoscopy.

Materials and Methods

Participants

This study was approved by the Ethics Committee of Zigong Hospital of Traditional Chinese Medicine (TCM) (2023 Quick Approval NO.1) and all participating patients signed an informed consent form. It was a prospective, double-blind, randomized controlled trial conducted at Zigong Hospital of TCM between December 2023 and April 2024. The study focused on patients scheduled for elective, painless colonoscopy procedures. The trial was registered at the Chinese Clinical Trial Registry (https://www.chictr.org.cn/; Registration number: ChiCTR2300077886) and followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for trial reporting. Additionally, the study conformed to the Declaration of Helsinki.

Inclusion Criteria

1) Age between 65 and 85 years; 2) American Society of Anesthesiologists (ASA) classification I or II; 3) Body Mass Index (BMI) from 18.5 to 23.9 kg/m².

Exclusion Criteria

1) Impaired liver or kidney function; 2) History of alcohol or opioid abuse; 3) Recent use (within three months) of benzodiazepines or analgesics; 4) Known allergies or contraindications to trial medications; 5) Patients requiring

intubation or identified as high-risk for airway management complications (eg, Mallampati score of 3 or 4); 6) Presence of psychiatric conditions or uncooperative attitude.

Withdrawal Criteria

1) Voluntary patient withdrawal at any time during the trial; 2) Necessity for additional endoscopic interventions; 3) Development of adverse reactions that necessitate stopping the procedure; 4) Occurrence of surgical complications, such as gastrointestinal perforation.

Randomization and Blinding

A total of 722 patients were randomly allocated in a 1:1 ratio into either the remimazolam + esketamine (RE) group or the propofol + esketamine (PE) group using the random grouping feature of SPSS version 27.0, operated by a professional not involved in the subsequent trial. The group assignments were sealed in opaque envelopes that were only opened by the anesthesiologist in charge before surgery to prepare the medication. The collection of data was conducted by another anesthesiologist. To ensure blinding of both patients and the data recording staff, due to the noticeable visual differences between propofol and remimazolam solutions, coverings were employed to conceal both the drugs and the intravenous setup; only the anesthesiologist in charge could see the actual medications. The group information was revealed only in cases of severe adverse events (such as cardiac arrest, respiratory depression requiring intubation, major gastrointestinal bleeding, or intestinal perforation), at which point the patient was withdrawn from the trial.

Sample Size Calculation

Based on the expected incidence of hypotension, with rates derived from previous literature and a pilot study (6.3% for PE and 1.2% for RE),and using PASS version 15.0 with a significance level (α) of 0.05 (two-sided) and power (β) of 0.9, each group required 328 participants.[10,12] Factoring in a 10% potential dropout rate, the total sample size was set at 722 patients (361 per group).

Procedure and Interventions

Patients were instructed to fast for 8 hours and abstain from liquids for 2 hours before the procedure, with no preoperative medication administered. Upon arrival, a 20G cannula was inserted for venous access, and oxygen was supplied at 4L/min via a nasal cannula. Continuous monitoring of blood pressure, ECG, respiratory rate, and oxygen saturation was conducted using a CNAP monitor.

Anesthesia was consistently administered by the same senior anesthesiologist. Before induction, patients were positioned with their heads in the "sniffing" position. In the remimazolam + esketamine (RE) group, patients first received a slow intravenous injection of 0.3 mg/kg esketamine followed by 0.15 mg/kg remimazolam within 30 seconds.[13] In the propofol + esketamine (PE) group, patients were administered 0.3 mg/kg esketamine and 1.5 mg/kg propofol within the same timeframe.[14] The anesthesiologist assessed the patient's level of sedation every 10 seconds using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale. Endoscopic procedures commenced when the MOAA/S score was ≤3.

All endoscopic examinations were performed by the same experienced endoscopist. If a patient's MOAA/S score rose above 3, or if coughing or movement occurred, additional doses of 0.05 mg/kg remimazolam or 0.5 mg/kg propofol were administered accordingly. In cases where sufficient anesthesia was not achieved within 15 minutes after induction, despite five supplemental doses, 0.5 mg/kg propofol was used as a rescue medication. During prolonged procedures, or if signs of inadequate analgesia (such as facies dolorosa or significantly increased respiratory rate) were observed, an additional 0.15 mg/kg esketamine was administered.

Post-procedure, patients were immediately transferred to the Post-Anesthesia Care Unit (PACU), where they were stimulated every two minutes until fully awake. Discharge from the PACU was based on a modified Aldrete score of ≥9.

Management of Adverse Events During Procedures

During surgery, if a patient experienced hypotension, characterized by a systolic pressure below 90 mmHg, a diastolic pressure below 60 mmHg, or a decrease of more than 20% from the baseline, an intravenous push of 20 μg of norepinephrine was administered.

For instances of hypertension, where the systolic pressure was 180 mmHg or higher, diastolic pressure was 110 mmHg or higher, or there was an increase of over 20% above baseline levels, 5 mg of urapidil was administered intravenously.

If bradycardia occurred, indicated by a heart rate below 50 bpm or a 20% reduction from the baseline, 0.25 mg of atropine was administered intravenously.

For tachycardia, with heart rates exceeding 100 bpm or increasing more than 20% from baseline, 0.5 mg/kg of esmolol was given intravenously.

Should respiratory depression have occurred (respiratory rate less than 8 breaths per minute or oxygen saturation below 90%), the oxygen flow was increased and the jaw was elevated. If after 10 seconds the condition did not improve, a nasopharyngeal airway or a simple respirator for assisted ventilation was employed. Tracheal intubation was considered if necessary.

Heart rate and blood pressure fluctuations resulting from inadequate sedation or pain management were not classified as adverse events if they stabilized following the administration of supplemental doses or rescue medications.

Outcome Measures

Primary Outcome Measures

Instances of hypotension during surgery (number and frequency).

Secondary Outcome Measures

1. Occurrences of hypertension, tachycardia, and bradycardia during surgery;
2. Usage of norepinephrine, urapidil, atropine, and esmolol during surgery;
3. Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) at key time points: at room entry (T_0), immediately after induction of anesthesia (T_1), at the start of the procedure (T_2), upon reaching the cecum (T_3), at the end of the procedure (T_4), upon awakening (T_5), and upon exiting the room (T_6);
4. Effectiveness of single-dose sedation, defined by the completion of the procedure, no emergency sedatives needed, and a maximum of five additional doses within 15 minutes post-initial dose.[15]
5. Usage of supplemental and rescue medications, noting the dosages;
6. Anesthesia induction time from drug administration to when the patient's MOAA/S score falls below 3;
7. Anesthesia recovery time from the last drug injection to when the MOAA/S score reaches 5;
8. The time taken from the last drug injection until the patient's Aldrete score is 9 or higher; and
9. Other adverse events such as respiratory depression, blurred vision, injection pain, nausea, vomiting, agitation during recovery, delirium, and hallucinations.

Additional Records

Oxygen saturation, respiratory rate at entry, duration of the procedure, and esketamine usage during surgery.

Statistical Methods

Data analysis was performed using SPSS software, version 27.0. Measurement data are presented as means ± standard deviations. First, a Kolmogorov–Smirnov test was conducted to assess the normality of the data, followed by a Levene's test to evaluate the homogeneity of variances. If both conditions were met, between-group comparisons were conducted using Student's *t*-test, and within-group comparisons were performed using the paired *t*-test. If these conditions were not satisfied, between-group comparisons were made using the Mann–Whitney *U*-test, and within-group comparisons were conducted using the Wilcoxon rank-sum test. Enumeration data are expressed as frequencies (percentages). Pearson's

chi-square test was used for non-ranked data, and the Mann–Whitney *U*-test for ranked data. A *p*-value of less than 0.05 was considered statistically significant. All data are reported to two decimal places.

Results

A total of 778 patients were initially included in this study. Exclusions were made for 16 patients at high risk of difficult airway, 4 with renal dysfunction, 3 with liver dysfunction, and 1 with a history of alcoholism, leaving 754 patients eligible for randomization into two groups: the RE group and the PE group. Due to the need for colon polyp removal, 51 patients withdrew from the study (19 from the RE group and 32 from the PE group). An additional patient was lost to follow-up due to delayed record keeping, resulting in 702 patients completing the trial. (Figure 1).

Baseline Characteristics

There were no significant differences ($P>0.05$) between the two groups in terms of baseline parameters and demographic features (age, gender, height, weight, ASA classification, or medical history). (Table 1).

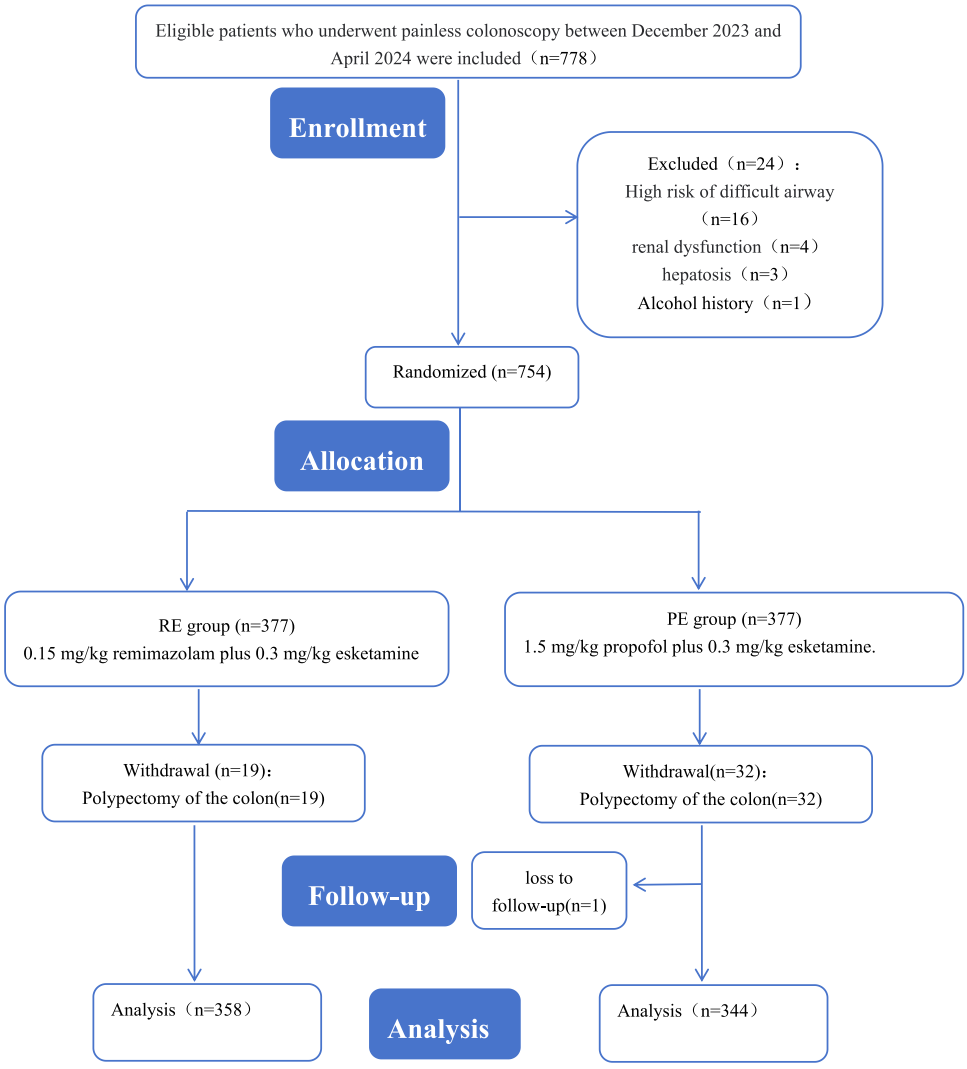

Figure 1 Patient flowchart with CONSORT guidelines.

Table 1 Baseline Characteristics

	RE Group N = 358	PE Group N = 344	*P*-value
Age (years)	74.68±6.03	75.21±5.98	0.25
Gender (Male/Female)	156/202	166/178	0.21
Height (cm)	162.66±5.84	162.48±5.54	0.58
Weight (kg)	56.30±5.85	55.92±5.42	0.63
ASA Classification (I/II)	25/333	35/309	0.13
Hypertension (cases (%))	244 (68.16)	215 (62.50)	0.12
Diabetes (cases (%))	91 (25.42)	67 (19.48)	0.06
COPD (cases (%))	35 (9.78)	46 (13.37)	0.14
Cerebrovascular Disease (cases (%))	18 (5.03)	15 (4.36)	0.66
Coronary Heart Disease (cases (%))	20 (5.59)	16 (4.65)	0.57
History of Surgery (cases (%))	158 (44.13)	130 (37.79)	0.09
Smoking (cases (%))	117 (32.68)	121 (35.17)	0.49
Alcohol Consumption (cases (%))	14 (3.91)	8 (2.33)	0.23
Motion Sickness (cases (%))	58 (16.20)	59 (17.15)	0.74

Notes: Measurement Data: Presented as mean ± standard deviation. Height was analyzed using the *t*-test, while other variables used the Mann–Whitney *U*-test;Enumeration Data: Presented as frequency or frequency (percentage), analyzed using the Pearson chi-square test.
Abbreviations: ASA, American Society of Anesthesiologists; COPD, Chronic Obstructive Pulmonary Disease; RE,0.15 mg/kg remimazolam plus 0.3 mg/kg esketamine; PE, 1.5 mg/kg propofol plus 0.3 mg/kg esketamine.

Hemodynamic Effects

No cases of hypertension were reported in either group. The incidence of intraoperative hypotension was significantly lower in the RE group compared to that in the PE group ($P<0.001$). The occurrence of intraoperative sinus tachycardia was also lower in the RE group than in the PE group ($P<0.001$). Similarly, intraoperative sinus bradycardia was less frequent in the RE group compared to that in the PE group ($P<0.001$). (Table 2).

Table 2 Adverse Reactions

	RE Group (n = 358)	PE Group (n = 344)	*P*-value
Hypotension	35 (9.78)	89 (23.57)	<0.001
95% CI	6.67–12.87%	21.22–30.52%	
Sinus Tachycardia	2 (0.56)	41 (11.92)	<0.001
95% CI	−0.22–1.33%	8.48–15.36%	
Sinus Bradycardia	13 (3.63)	72 (20.93)	<0.001
95% CI	1.68–5.58%	16.61–25.25%	
Respiratory Depression	8 (2.23)	22 (6.40)	0.006
Injection Pain	0 (0)	131 (38.08)	<0.001
Blurred Vision	19 (5.31)	26 (7.56)	0.23
Nausea and Vomiting	11 (3.07)	14 (4.36)	0.37
Agitation during Recovery	16 (4.47)	13 (3.78)	0.65
Delirium	11 (3.07)	9 (2.62)	0.72
Hallucinations	8 (2.23)	4 (1.62)	0.27
Norepinephrine (ug)	2.35±7.57	6.51±12.10	<0.001
Atropine (mg)	0.01±0.047	0.05±0.10	<0.001
Esmolol (mg)	0.16±2.12	1.99±7.31	<0.001

Notes: Measurement Data: Presented as mean ± standard deviation; analyzed using the Mann–Whitney *U*-test; Enumeration Data: Presented as frequency (percentage), analyzed using the Pearson chi-square test.
Abbreviations: CI, Confidence Interval; RE, 0.15 mg/kg remimazolam plus 0.3 mg/kg esketamine; PE, 1.5 mg/kg propofol plus 0.3 mg/kg esketamine.

During the surgical procedures, none of the patients in either group received urapidil. There were significant statistical differences in the usage of norepinephrine, atropine, and esmolol between the groups ($P<0.001$) as detailed in Table 2.

At T_0 and T_6, there were no statistically significant differences in systolic or diastolic blood pressure between the two groups ($P>0.05$). However, between T_1 and T_5, both systolic and diastolic pressures were consistently higher in the RE group ($P<0.001$). Specifically, systolic pressures at T_1 were 131.25 ± 10.87 mmHg in the RE group vs 126.99 ± 11.21 mmHg in the PE group. This trend continued at subsequent time points: T_2 showed 115.45 ± 7.77 mmHg in the RE group compared to 110.46 ± 8.77 mmHg in the PE group; T_3, 115.43 ± 9.34 mmHg vs 111.77 ± 10.36 mmHg; T_4, 116.15 ± 10.91 mmHg vs 111.01 ± 11.79 mmHg; and T_5, 126.98 ± 11.01 mmHg vs 123.45 ± 10.15 mmHg.(Figure 2a)

For diastolic pressures, the findings were similar with T_1 measurements at 80.34 ± 5.84 mmHg in the RE group vs 77.70 ± 5.97 mmHg in the PE group. This pattern persisted at T_2 (70.85 ± 5.24 mmHg vs 67.39 ± 4.29 mmHg); T_3 (70.65 ± 5.34 mmHg vs 68.31 ± 5.35 mmHg); T_4 (71.19 ± 5.96 mmHg vs 67.66 ± 5.89 mmHg); and T_5 (76.84 ± 6.08 mmHg vs 74.60 ± 5.35 mmHg). (Figure 2b)

In the RE group, significant increases in both systolic and diastolic pressures were observed from T_0 to T_1, T_4 to T_5, and T_5 to T_6 ($P<0.001$), with a significant decrease from T_1 to T_2 ($P<0.001$). Conversely, in the PE group, systolic pressure slightly decreased from T_0 to T_1 ($P=0.045$) and showed significant decreases from T_1 to T_2 ($P<0.001$), T_3 to T_4 ($P=0.001$), with significant increases from T_2 to T_3 ($P=0.006$), T_4 to T_5 ($P<0.001$), and T_5 to T_6 ($P<0.001$). Diastolic pressure in the PE group significantly decreased from T_1 to T_2 ($P<0.001$) and showed significant increases from T_3 to T_4, T_4 to T_5, and T_5 to T_6 ($P<0.001$). (Figure 2c and d).

Heart rate measurements at T_0, T_1, and T_6 showed no significant differences between the two groups ($P>0.05$). At T_2, the heart rate in the RE group was significantly lower than in the PE group, with a mean difference of −7.00 bpm ($P<0.001$). From T_3 to T_6, the heart rate in the RE group was higher than in the PE group, with mean differences of 4.76 bpm, 2.74 bpm, 2.12 bpm, and 2.52 bpm, respectively (all $P<0.001$). (Figure 3a).

In the RE group, there were significant increases in heart rate from T_0 to T_1, T_4 to T_5, and T_5 to T_6 ($P<0.001$), and significant decreases from T_1 to T_2, T_2 to T_3, and T_3 to T_4 ($P<0.001$) (Figure 3b). In the PE group, heart rate significantly increased from T_0 to T_1, T_1 to T_2, T_4 to T_5, and T_5 to T_6 ($P<0.001$), with significant decreases from T_2 to T_3 and T_3 to T_4 ($P<0.001$) (Figure 3c).

Sedation Outcomes

Both groups achieved a 100% sedation success rate. There were no significant differences in the duration of surgery or the amount of esketamine used ($P>0.05$). However, induction time was longer in the RE group ($P<0.001$), and they required more supplemental doses ($P<0.001$). Recovery and room exit times were also significantly shorter in the RE group compared to the PE group ($P<0.001$). (Table 3).

Adverse Reactions

No significant differences were observed in respiratory rate and oxygen saturation upon room entry ($P>0.05$). Injection pain was reported in the PE group but not in the RE group ($P<0.001$). Respiratory depression occurred in RE group was less frequent in the PE group ($P=0.006$). Other adverse reactions, including blurred vision, nausea, vomiting, agitation during recovery, delirium, and hallucinations, showed no significant differences between the groups ($P>0.05$). (Table 2).

Discussion

This study primarily investigates the hemodynamic effects of remimazolam and propofol combined with esketamine during painless colonoscopy procedures in elderly patients. Our findings indicate that remimazolam provides superior stability in hemodynamics compared to propofol, resulting in lower incidences of hypotension, sinus tachycardia, and sinus bradycardia. Additionally, remimazolam is associated with the absence of injection pain. Notably, while remimazolam shows a longer induction time, it facilitates a quicker recovery.

Despite the abundance of research comparing remimazolam and propofol, outcomes are varied and inconsistent. Furthermore, there are no existing studies on the use of esketamine combined with these agents for painless colonoscopy

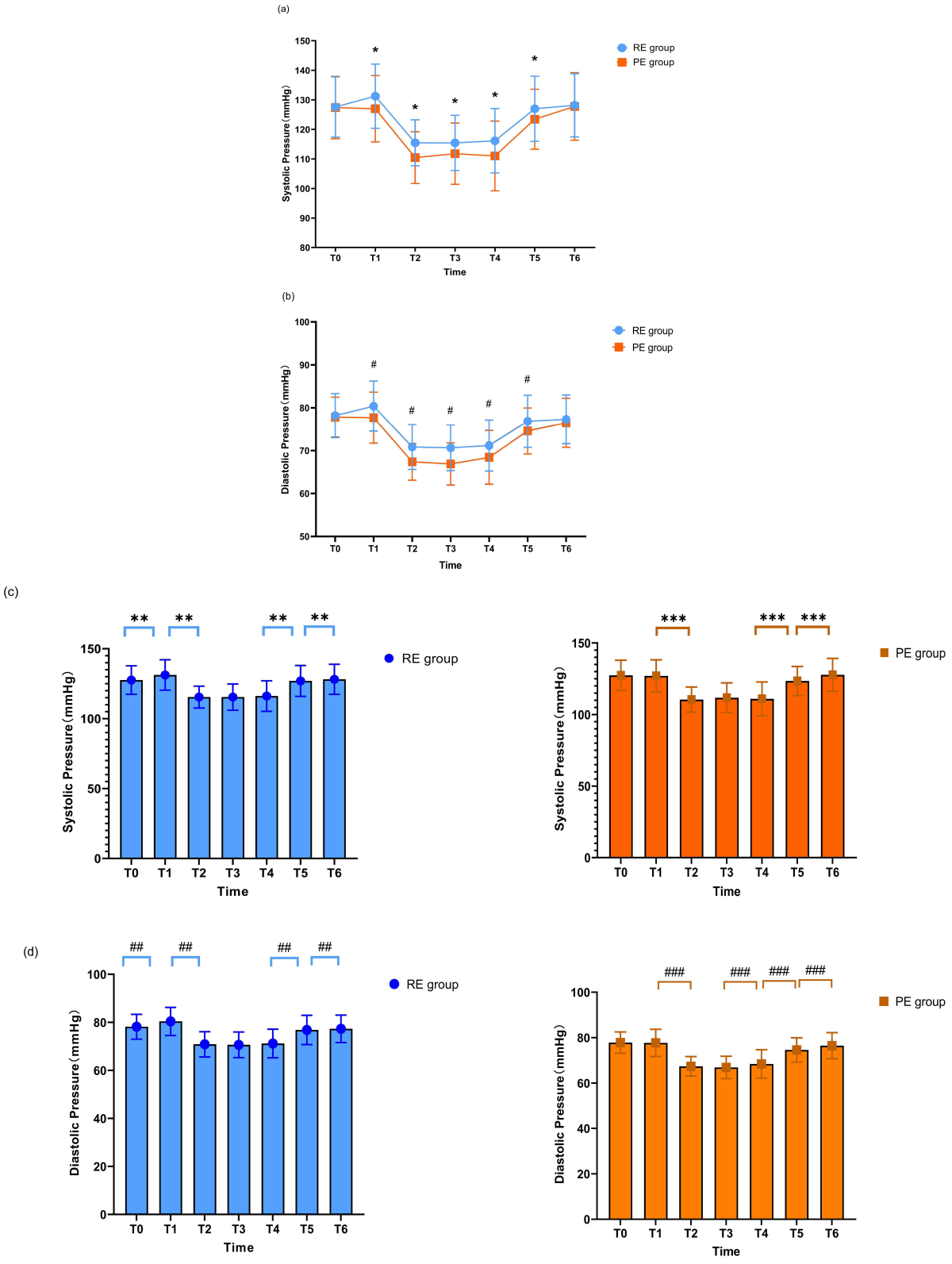

Figure 2 Blood Pressure Comparison Between Two Patient Groups. Depending on the normality of data distribution, either Student's *t*-test or the Mann–Whitney *U*-test was employed.Within-group Comparisons: The paired *t*-test or the Wilcoxon signed-rank test was utilized. (**a**) Systolic Blood Pressure Comparison Between Groups: *P<0.001; (**b**) Diastolic Blood Pressure Comparison Between Groups: $^{\#}P$<0.001; (**c**) Systolic Blood Pressure Comparison Within Each Group: **P<0.001,***P<0.001; (**d**) Diastolic Blood Pressure Comparison Within Each Group: $^{\#\#}P$<0.001,$^{\#\#\#}P$<0.001; T_0: at room entry; T_1: immediately after induction of anesthesia; T_2: at the start of the procedure; T_3: upon reaching the cecum; T_4: at the end of the procedure; T_5: upon awakening; T_6: upon exiting the room. RE:0.15 mg/kg remimazolam plus 0.3 mg/kg esketamine; PE:1.5 mg/kg propofol plus 0.3 mg/kg esketamine.

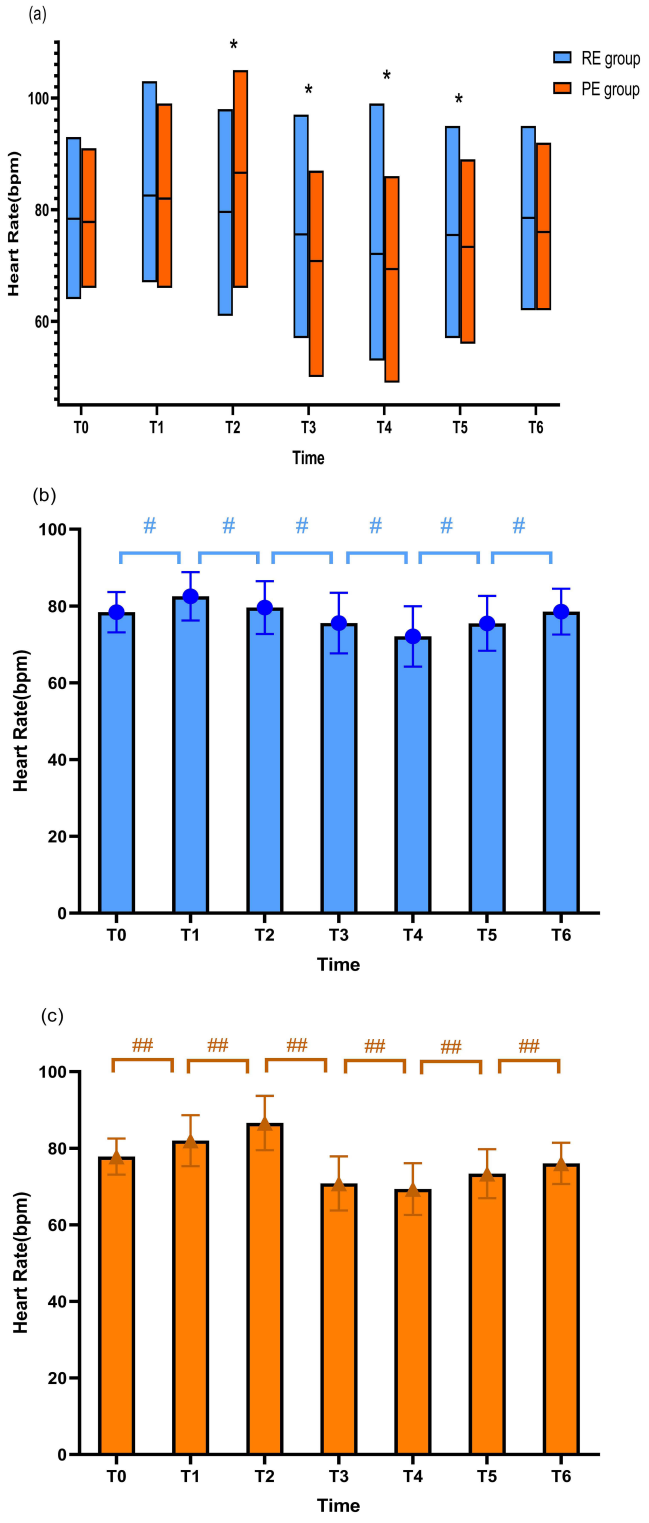

Figure 3 Comparison of Heart Rate Between Two Patient Groups. Depending on the normality of data distribution, either Student's *t*-test or the Mann–Whitney *U*-test was used;Within-group Comparisons: The paired *t*-test or the Wilcoxon signed-rank test was applied. (**a**) Heart rate comparison between the two groups: $^{*}P<0.001$; (**b**) Within-group comparison of heart rate in the RE group: $^{\#}P<0.001$; (**c**) Within-group comparison of heart rate in the PE group: $^{\#\#}P<0.001$; T_0: at room entry; T_1: immediately after induction of anesthesia; T_2: at the start of the procedure; T_3: upon reaching the cecum; T_4: at the end of the procedure; T_5: upon awakening; T_6: upon exiting the room. RE:0.15 mg/kg remimazolam plus 0.3 mg/kg esketamine; PE:1.5 mg/kg propofol plus 0.3 mg/kg esketamine.

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Table 3 Sedation Details

	RE Group (N = 358)	PE Group (N = 344)	*P*-value
Surgery Duration (min)	12.54±1.59	12.42±1.64	0.39
Esketamine Dose (mg)	17.25±2.41	17.22±2.54	0.66
Induction Time (S)	46.70±4.77	31.51±3.59	<0.001
Additional Medication Administration (times)	0 (0)/1 (146)/2 (212)	0 (63)/1 (179)/2 (102)	<0.001
Recovery Time (min)	13.92±1.17	19.43±1.17	<0.001
Room Exit Time (min)	29.43±2.38	36.89±2.26	<0.001

Notes: Measurement Data: Presented as mean ± standard deviation. Surgery duration was analyzed using the *t*-test, while other variables used the Mann–Whitney *U*-test; Enumeration Data: Presented as frequency, analyzed using the Mann–Whitney *U*-test.
Abbreviations: RE, 0.15 mg/kg remimazolam plus 0.3 mg/kg esketamine; PE, 1.5 mg/kg propofol plus 0.3 mg/kg esketamine.

in the elderly—a gap that underscores the importance and clinical relevance of our investigation, given the unique physiological characteristics of this age group.

Regarding dosages, we adhered to the protocol established by Guo et al, administering remimazolam at 0.15 mg/kg.[13] Employing Dixon's up-and-down method, Zheng et aldetermined the effective doses (ED50% and ED90%) for propofol in painless gastroscopy and colonoscopy among elderly patients, leading us to administer 1.5 mg/kg of propofol and 0.3 mg/kg of esketamine.[14]

We employed a continuous non-invasive arterial pressure monitoring system that also offers the benefits of invasive monitoring without the risk of puncture injuries. This system revealed a potentially overlooked phenomenon in previous studies—that both remimazolam and propofol might induce a higher incidence of hypotension than previously reported. Traditional studies frequently used basic non-invasive blood pressure monitoring, focusing only on specific time points. This approach can diminish the immediacy and accuracy of data, potentially missing some instances of hypotension. During the trial, we observed that some patients developed hypotension prior to the scheduled monitoring times. Particularly, in patients whose blood pressure was just below the critical thresholds, there tended to be a recovery in blood pressure levels, likely due to surgical stimulation occurring around the T_2 time point.

In our study, nearly 10% of patients in the remimazolam group experienced hypotension, compared to nearly 25% in the propofol group—a significant increase over the rates reported by Yue et al.[16] We hypothesize that this discrepancy may be due to diminished sympathetic regulation in elderly patients. Additionally, the lack of anesthesia depth monitoring raises concerns that the dosages of 0.15 mg/kg remimazolam plus 0.3 mg/kg esketamine, and 1.5 mg/kg propofol plus 0.3 mg/kg esketamine, may be excessive.

Contrasting with the findings of Li et al, where two groups showed blood pressure differences at only two of eight monitoring points, our study demonstrates that blood pressure from T_1 to T_5 was consistently better managed in the remimazolam group (RE) than in the propofol group (PE).[11] This suggests that remimazolam can provide a stronger and more consistent stabilization of blood pressure in elderly patients compared to younger counterparts. However, the observed differences in mean systolic and diastolic pressures at these points appear clinically insignificant (the largest mean difference in systolic pressure being 5.14 mmHg, and in diastolic pressure, 3.53 mmHg), likely due to our timely interventions upon detecting hypotension. Thus, we recommend routine administration of norepinephrine when necessary to manage such events effectively.

Previous research results showed that patients using remimazolam combined with esketamine experienced an average increase of 24% in heart rate from induction to the start of surgery, and throughout the experiment, their heart rates were higher than those of patients using propofol.[16] However, we observed two interesting phenomena in our trial. Firstly, unlike at T_3 and T_4, the heart rate in the RE group was actually lower than in the PE group at T_1 and T_2. Correspondingly, the incidence of sinus tachycardia in the PE group (mainly at T_2) was significantly higher than in the RE group, and the occurrence of sinus bradycardia (mainly at T_3 and T_4) was also higher in the PE group. We consider this might be due to the injection pain of propofol stimulating the sympathetic nervous system and the balancing effect of remimazolam on sympathetic and parasympathetic activities during induction, whereas propofol's regulation resulted in sympathetic

dominance.[17] As sedation deepened, the parasympathetic dominance of propofol became apparent. Secondly, the heart rate of patients in the propofol group during the recovery phase (T_5, T_6) remained lower than that of the RE group, possibly because the suppression of the baroreflex by propofol took 60 minutes to recover after stopping the drug.[18] This indicates a stronger stabilizing effect of remimazolam on heart rate.

We also explored the induction and recovery times of remimazolam in our trial. Previous studies seem to have conflicting results regarding induction and recovery times.[11,16,19,20] Firstly, we concluded that remimazolam's induction time was significantly prolonged (about 15 seconds on average). Secondly, regarding recovery time, we believe that the recovery time of remimazolam was significantly reduced. This corresponds with the frequency of additional sedatives administered during the procedure. The reasons for this might be complex, including different metabolic paths of the drugs, differences in study subjects, methods of administration, etc. Given remimazolam's rapid recovery characteristics — achieving full alertness (MOAA/S score of 5) just 19 minutes after ceasing a 35-minute IV infusion — the use of flumazenil is unnecessary in clinical practice.[9] Additionally, flumazenil administration could potentially influence the trial outcomes, as the PE group did not receive a corresponding antagonist.

Sedation-related complications also consistently remain a focus of concern for anesthesiologists, as a high rate of complications can limit the clinical use of the drugs. Consistent with previous study results, the incidence of respiratory depression was lower in the RE group.[21] Even though esketamine can reduce the injection pain of propofol, compared to the fact that no patients in the RE group experienced injection pain, the results of the PE group were significantly inferior.[22] The incidence of other adverse events was also within clinically acceptable ranges.

This study still has some limitations. Firstly, as previously mentioned, due to conditional restriction, we lacked monitoring of anesthesia depth in our trial. This might have led to excessively deep anesthesia, and in colonoscopy examinations, it is not clear if 1.5 mg/kg of propofol is equivalent to 0.15 mg/kg of remimazolam for elderly patients. We could only observe that both dosages met clinical needs. Secondly, we used an intermittent additional dosing method, not continuous infusion. Severe fluctuations in plasma drug concentrations could significantly affect the stability of hemodynamics. However, the dosing method we used is still commonly employed in most hospitals in China. Finally, this study only targeted elderly patients aged between 65 and 85, with ASA grades I—II. Whether the results are also appropriate for very elderly patients or those with ASA grades III and above remains uncertain. More trials are needed to verify this.

Conclusion

Compared to propofol, remimazolam demonstrates superior hemodynamic stability with a significantly lower incidence of adverse events such as hypotension, sinus tachycardia, and sinus bradycardia. Although the onset of action for remimazolam is marginally slower than that of propofol, it offers a notably quicker recovery time. Additionally, remimazolam substantially reduces the risks of respiratory depression and injection pain. This regimen is recommended as an effective anesthesia strategy for painless colonoscopy procedures in elderly patients.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics

This trial was registered in the China Clinical Trial Registry on 22/11/2023 (Registration number: ChiCTR2300077886). The study was approved by the Ethics Committee of Zigong Hospital of Traditional Chinese Medicine (TCM) (2023 Quick Approval NO.1). Written informed consent was obtained from all participants. This study was conducted following the CONSORT extension for abstracts.

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Disclosure

The authors report no conflicts of interest in this work.

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