Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Etomidate Combined with Propofol versus Remimazolam for Sedation in Elderly Patients During Gastrointestinal Endoscopy: A Randomized Prospective Clinical Trial

Qin Zhang[1], Rui Zhao[1], Yaqing Wu[2], Liming Zhang[1], Yi Feng[2]

[1]Endoscopy Center, Peking University People's Hospital, Beijing, People's Republic of China; [2]Department of Anesthesiology, Peking University People's Hospital, Beijing, People's Republic of China

Correspondence: Yi Feng, Department of Anesthesiology, Peking University People's Hospital, Beijing, 100044, People's Republic of China, Email doctor_yifeng@sina.com

Purpose: Remimazolam is a novel short-acting benzodiazepine used for sedation and general anesthesia. This study aimed to evaluate the efficacy and safety of remimazolam besylate in elderly patients who underwent diagnostic gastrointestinal endoscopy.

Patients and Methods: A total of 120 patients aged 60–75 years were randomly allocated to one of two groups. Remifentanil 0.3μg/kg was used for analgesia. Patients were administered remimazolam besylate 7 mg (R group) or etomidate 0.1 mg/kg combined with 1% propofol 0.5 mg/kg (EP group) for induction, supplemental repeated doses were given as needed. Some time metrics, vital signs, adverse events were evaluated. Patients' Mini-cog score and recovery questionnaires were compared.

Results: Compared to the EP group, the induction time was slightly longer in the R group (1.50 VS 1.15 minutes) ($P<0.05$), the time spent in the post-anesthesia care unit (PACU) was shorter (15.17 VS 17.40 minutes) ($P<0.05$). Compare with EP group, SBP was lower in R group at T15 and T25 time point, but heart rate was higher in T2, T3, T5 ($P< 0.05$). The Mini-Cog score was higher after the procedure (2.83 VS 2.58) ($P<0.05$). The incidence of respiratory adverse events was higher in the EP group than R group (18.3% VS 5.0%, $P < 0.05$). The most common adverse event in R group was hiccups. The sedation satisfaction rate and degree of amnesia were higher in the R group (66.7% VS 11.7%) ($P < 0.05$), and the effect on patient's life within 24 hours was lower (12.0% VS 30.5%) ($P < 0.05$).

Conclusion: The safety and efficacy of remimazolam besylate are not inferior to those of etomidate combined with propofol, rendering it a safe option for sedation during gastrointestinal endoscopy in ASA I-II elderly patients, but care should be taken to monitor the occurrence of hiccups.

Keywords: gastrointestinal endoscopy, anesthesia, remimazolam besylate, etomidate, propofol

Introduction

An aging population's share rises in tandem with social productivity. Gastrointestinal endoscopy is a reliable method for the diagnosis of gastrointestinal diseases. However, gastrointestinal endoscopic stimulation can result in a variety of symptoms including nausea, vomiting, abdominal distension, abdominal pain, elevated blood pressure, and arrhythmia. Under extreme circumstances, it can cause cerebral infarction, myocardial ischemia, and other cardiovascular and cerebrovascular accidents, endangering the physiological and psychological well-being.[1] Anesthesia is becoming more and more popular among the elderly people every year. Currently, midazolam and propofol are the most commonly used sedatives for anesthesia during gastrointestinal endoscopic operations. Anterograde amnesia, steady circulation, mild respiratory depression, and good sedative effects are some benefits of midazolam. However, midazolam increases the metabolic time of the elderly, and patients recover slowly.[2] In contrast, propofol has a quick onset and recovery. Nonetheless, there is a chance that respiratory circulation will be inhibited, putting elderly surgical patients undergoing

Received: 11 December 2023
Accepted: 25 June 2024
Published: 2 July 2024

outpatient care at risk.[3,4] Anesthesiologists have optimized medication regimes to minimize respiratory and circulatory depression without affecting postoperative cognitive function, thus achieving safe, efficient, and high-quality recovery.

Remimazolam, a class 1.1 novel drug that acts on GABA receptors, has the advantages of midazolam. Unlike midazolam, remimazolam is metabolized by plasma esterase, and its metabolism time is only 1/7 that of midazolam. Remimazolam offers clear benefits to older patients with liver and kidney disease, remimazolam offers clear benefits.[5,6] Studies of outpatient mini-surgery have demonstrated its benefits in terms of quick recovery and safety.[7] The impact of remimazolam sedation on the recovery time of gastrointestinal endoscopy in elderly patients remains uncertain, as does its potential to enhance patient satisfaction and influence cognitive function in this population. Remifentanil is an opioid μ-receptor agonist narcotic analgesic with rapid onset, short recovery time, and its clearance rate is not affected by liver and kidney function. Remifentanil is metabolized by non-specific lipase in red blood cells and tissues without accumulation, which is suitable for outpatient anesthesia in elderly patients. However, few studies have investigated the use of remimazolam combined with remifentanil in gastrointestinal endoscopy in elderly patients. Propofol combined with etomidate injection is commonly used for gastrointestinal endoscopy in elderly patients under reliable sedation. A meta-analysis involving 15 studies and 2973 patients showed that the use of etomidate combined with propofol in endoscopy was safer and had a lower incidence of hypoxia and hypotension than propofol alone.[8] In this study, a combination of etomidate and propofol was used as a control and compared with remimazolam in elderly patients undergoing gastrointestinal endoscopy anesthesia, the effect on patients' cognitive aspects, satisfaction and postoperative 24h follow-up survey. This study aimed to further optimize anesthesia protocols and provide a basis for clinical studies.

Materials and Methods

Patients

This single-center randomized controlled trial included Patients aged 60–75 with ASA grade I–II (The American Society of Anesthesiologists physical status) who underwent gastroscopy, colonoscopy, or both under anesthesia at the Endoscopy Center of Peking University People's Hospital between October 2021 and April 2022. The exclusion criteria were allergy to drugs used in this study or soybean oil or fat emulsion, recent upper respiratory tract infection or asthma attack, history of addiction to opiates and/or sedatives (hypnotics), and advanced tumor with extensive intraperitoneal metastasis. All the endoscopic Procedures were performed by experienced endoscopists. The patients who underwent both gastroscopy and colonoscopy underwent gastroscopy first, and then underwent colonoscopy after bed transfer. This study was approved by the Ethics Committee of the Peking University People's Hospital (2021PHB002-001) and Clinical Trail.gov ID NCT05103696. Written informed consent was obtained from all the patients prior to the procedure. This study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and the Declaration of Helsinki.

Randomization and Blinding

Patients were randomly assigned to one of the two sedation protocols using a computer-generated random sequence. Owing to the different appearances of the two drugs, a single-blind design was adopted for this study. All endoscopists, nurses, and patients were blinded to group allocation.

Procedures

All the patients underwent bowel preparation according to the standard protocol. Supplemental oxygen at a rate of 4 L/min by nasal cannula was administered to all patients immediately after they entered the examination room until they were fully alert, according to sedation guidelines. The patients underwent ASA standard monitoring (blood pressure, heart rate [HR], pulse oxygen saturation, and end-tidal carbon dioxide through nasal microstream $EtCO_2$ consumables). The timing was started at the beginning of the sedative injection. Basic hemodynamic were recorded as T0, then every minute for the first 3 min, after that record once every 5 min as T1, T2, T3, T5, T10…. Remifentanil 0.3μg·kg-1 body weight (injection time: 60s) was administered by intravenous bolus injection 1 min before the initiation of sedation. An endoscope can be inserted after the eyelash reflex has disappeared. In the EP group, etomidate 0.1 mg·kg-1 body

weight and 1% propofol 0.5 mg·kg-1 body weight were given intravenously for the first time. Sedation was maintained with repeated doses of propofol (10–20 mg) and etomidate (2–4 mg). In the R group, 7 mg of remimazolam adjuvant was administered intravenously for the first time, and sedation was maintained with repeated doses of remimazolam (2.5 mg) no more than 5 times over 15 min. Sedative drugs and remifentanil 10μg bolus per time were added according to the depth of anesthesia. The modified Observer's Assessment of Alertness/Sedation (MOAA/S) score was maintained at ≤4 throughout the entire process.[9] If the sedation protocol fails, a 10–20 mg bolus of propofol may be used as a rescue agent.

The anesthesiologist pays close attention to all monitoring parameters to ensure that the patient is anesthetized safely, with jaw support or advanced life support if necessary. Equipment for full resuscitation was available in the endoscopy unit at all times. Both flumazenil and naloxone can be used as reversal agents when severe adverse effects associated with remimazolam and opioids are suspected. After endoscopy, the patients were observed in the post-anesthesia care unit (PACU). The Aldrete score was calculated every 5 min after the completion of the procedure, and three consecutive scores ≥9 enabled patients to be discharged from the PACU.

Clinical Outcomes

The primary outcomes were time metrics as follows: induction time was defined as the time interval between "the start of the sedative injection" and "patients lost their eyelash reflex". Total procedure time was defined as the time interval between the "start of gastroscopy" and "endoscope removal". Voluntary eye-opening time was defined as the time interval between "discontinuation of the sedative injection" and "the patient opened her eyes voluntarily". Recovery time was defined as the time interval between "discontinuation of the sedative injection" and "patient reaching MOAA/S scale 5", which means that the patient responded appropriately to normal volume verbal cues by using either a verbal or physical response without delay or hesitation. Observation time in the PACU was defined as the time interval between "endoscope removal" and "endoscope departure from the recovery room".

The secondary outcomes were adverse effects, such as hypotension (SBP < 90 mmHg, DBP < 50 mmHg), bradycardia (< 50 beats per minute), hypertension (SBP > 180 mmHg, DBP> 110 mmHg), hypoxia (SpO_2 < 90% on 4 L/min oxygen), respiratory depression (respiratory rate < 8 breaths per minute), and prolonged sedation (MOAA/S score ≤ 4 for longer than 30 min after the end of the colonoscopy). The occurrence of adverse effects, coughs, body movements, tongue falls, hiccups, nausea, and dizziness was recorded.

Before discharge, patients were asked to fill out a short postoperative recovery questionnaire and use a standard 10 cm visual analog scale to report the pain intensity they experienced during the procedure and their overall satisfaction with the procedure. Patients were also followed-up by phone 24 h later, and a follow-up questionnaire was completed. The effects of anesthesia on cognitive function were recorded using the Mini-Cog score before anesthesia and before discharge.[10]

Statistical Analysis

R4.2.1 software was used for the statistical analysis. Normality of data and homogeneity of variance were tested using the *Shapiro–Wilk* test for normality and *Levenes* test for homogeneity of variances, respectively. Continuous variables with normal distribution were expressed as mean ± standard deviation and compared using the *t*-test. Non-normally distributed continuous data were summarized as median (interquartile range, IQR) and compared using the Mann–Whitney test., and statistical significance was set at P <0.05. The counts were expressed as frequencies or percentages, and a chi-square test or Fisher's exact probability method was used for comparison between the two groups. Statistical significance was set at P < 0.05.

The sample size was calculated on the basis of a previous study.[11] The recovery times in the EP and R group were 8.7 to 6.8 minutes. The predefined non-inferiority margin was an absolute difference of 5% between the groups for the primary endpoint. With a non-inferiority margin of 20% on the relative scale, power of 80%, and one-sided alpha of 2.5%, the total sample size required was 51. Assuming a dropout rate of 10%, a minimum of 60 patients were recruited for each group.

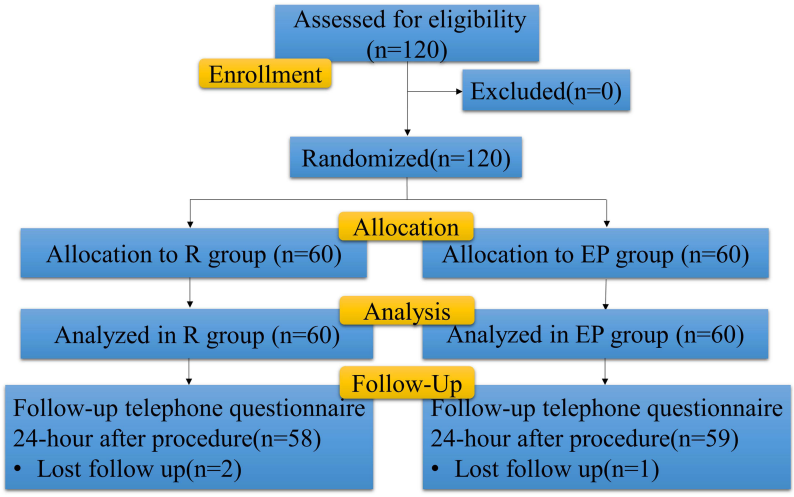

Figure 1 Study design: summary of inclusion and exclusion criteria of study population.

Results

A total of 120 patients were initially enrolled in the study; no patients were excluded, with 60 patients in each group (Figure 1). There were no significant differences in sex, age, BMI, procedure type, or ASA classification between the two groups (Table 1). The success rate of sedation was 98.3% in the EP group and 93.3% in the R group. One patient (1.7%) in the EP group and four (6.7%) in the R group used propofol as rescue, there was no significant difference between the two groups (P=0.17). The MOAA/S score of the R group was higher than that of the EP group 1 and 2 min after administration (P< 0.05) (Figure 2). After administration, the induction time in the R group was longer than that in the EP group (P<0.05). The observation time in the PACU was significantly shorter in the R group than in the EP group (P<0.05). The Mini-Cog score of the R group was higher than that of the EP group (P<0.05). There were no statistically significant differences in the consumption of sedatives and analgesics, pain scores, or physician satisfaction scores between the two groups (Table 2). SpO_2 fluctuated between 97% and 100% in both groups and decreased slightly 3 min after the first administration; Compared with the baseline value T0, $PetCO_2$ decreased within 1–10 min after the first dose in both groups (P <0.05) and decreased to the lowest level approximately 3 min after administration (Figure 3). However, there was no significant difference between the two groups at any time point (P≥0.05). Respiratory rates decreased from 1 to 5 min after the first dose in both the groups. The RR was lower in the EP group than in the R group in T3 (P<0.05) (Figure 4). Compared with T0, the heart rate of the EP group decreased significantly 5 min after the first dose (P< 0.05). Compared with patients in the EP group, those in the R group had a higher heart rate at T2, T3, T5 (P<0.05) (Figure 5). A change in blood pressure was observed in both groups. SBP decreased significantly 3–5 min after the first dose (P< 0.05) in both group, but higher in EP group than in R group at T15 and T25 (Figure 6). A comparison of adverse events between the two groups, hiccups were the most common adverse reaction in the R group, which was higher than that in

Table 1 Basic Characteristics of the Study Groups

	EP Group (n=60)	R Group (n=60)	P value
Type of procedure (Gastroscopy/ Colonoscopy/ Gastrointestinal endoscopy)	4/5/51	1/7/52	0.343
Sex (male/female)	24/36	22/38	0.851
Age	66.2±3.7	64.9±4.2	0.078
Body height (cm)	165.7±8.6	164.8±8.0	0.728
Body weight (kg)	65.6±10.0	65.8±11.0	0.927
BMI (kg/m^2)	23.8±2.9	24.1±2.7	0.755
ASA classification (grade I/II)	11/49	16/44	0.382

Abbreviations: BMI, body mass index; ASA, The American Society of Anesthesiologists physical status.

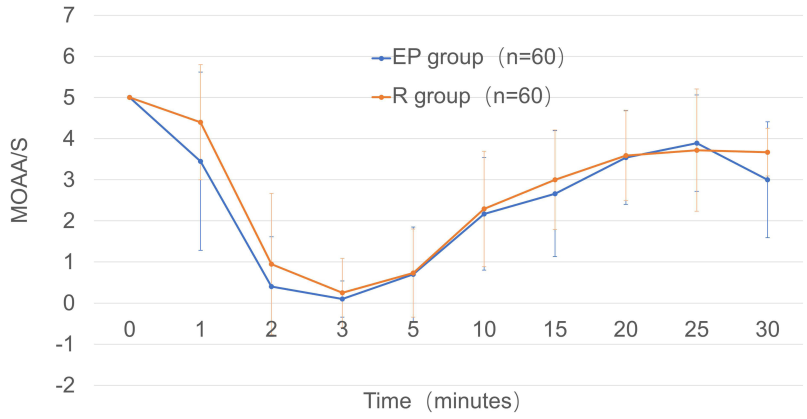

Figure 2 Comparison of MOAA/S score. The MOAA/S score of the R group was higher than that of the EP group at first 2min after administration (P< 0.05).

the EP group (P< 0.05). The total number of respiratory adverse events was higher in the EP group than in the R group (P< 0.05) (Table 3). The Results of comparison of follow-up questionnaire showed that there was a significant difference in the answer to the question "how was the sedation for your procedure?" between the two groups (Table 4) (P< 0.05). Endoscopic removal was observed in 84.5% of patients in the R group, which was higher than that in the EP group (P<0.05). In the R group, 87.9% thought that they were not affected by sedates, which was higher than that in the EP group (P<0.05) (Table 5).

Discussion

The purse of this study was to evaluate the efficacy and safety of remimazolam besylate for gastrointestinal endoscopy in elderly patients. Gastrointestinal endoscopy is a necessary screening tool for digestive system diseases and has become routine. Non-intubated intravenous general anesthesia is commonly used for gastrointestinal endoscopy, and sedation levels are maintained depending on the surgical procedure and patient's condition. The purpose of painless endoscopic anesthesia in the elderly patient is balancing the stress response induced by endoscopic surgical stimulation ensures patient stability and safety of breathing and circulation and reduces the occurrence of complications, rapid post-operative recovery, and safe discharge from the hospital.

Table 2 Comparison of Primary Outcomes

	EP Group (n=60)	R Group (n=60)	95% CI	P value
Induction Time (minute)	1.15±0.38	1.50±0.63	−0.54, −0.17	<0.001
Total procedure time (minute)	19.02±6.64	19.30±7.12	−2.77, 2.21	0.831
Voluntary eye-opening time (minute)	10.16±4.06	10.69±3.91	−1.97, 0.92	0.231
Recovery time (minute)	12.72±3.72	13.08±4.06	−1.77, 1.04	0.668
Observation time in the PACU (minute)	17.40±2.08	15.17±2.46	1.41, 3.06	<0.001
Mini-cog score	2.58±0.53	2.83±0.38	−0.42, −0.08	0.004
Consumption of sedatives, mL	9.74±2.07	9.93±2.02	−0.93, 0.55	0.768
Consumption of analgesics, μg	32.22±7.46	34.20±7.09	−4.61, 0.65	0.130
Consumption of analgesics (μg/kg/min)	0.027+0.01	0.031+0,01	−0.01, 0.00	0.199
Pain score	0.18±0.47	0.05±0.22	0.00, 0.27	0.065
Satisfaction score	9.83±0.42	9.93±0.31	−0.23, 0.03	0.075

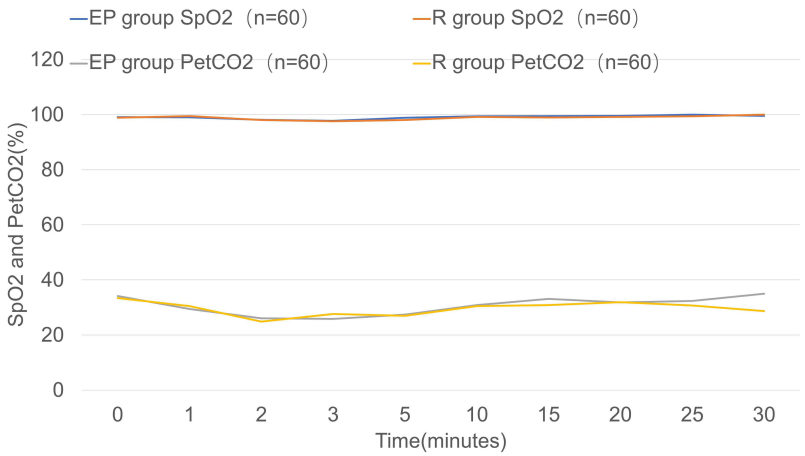

Figure 3 Comparison of SpO_2 and $PetCO_2$. There was no significant difference in SPO_2 between the two groups at each time point (P>0.05). Compared with the baseline value T0, $PetCO_2$ decreased within 1–10 min after the first dose in both groups (P <0.05) and decreased to the lowest level approximately 3 min after administration.

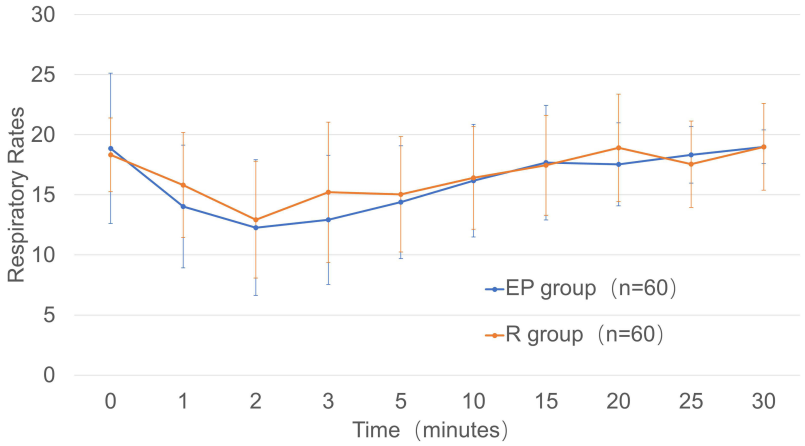

Figure 4 Comparison of respiratory rates. In both groups, respiratory rates decreased from 1 to 5 min after administration of the drug compared with baseline. It then returned to baseline levels. The RR was lower in the EP group than in the R group at 3 min after administration (P<0.05).

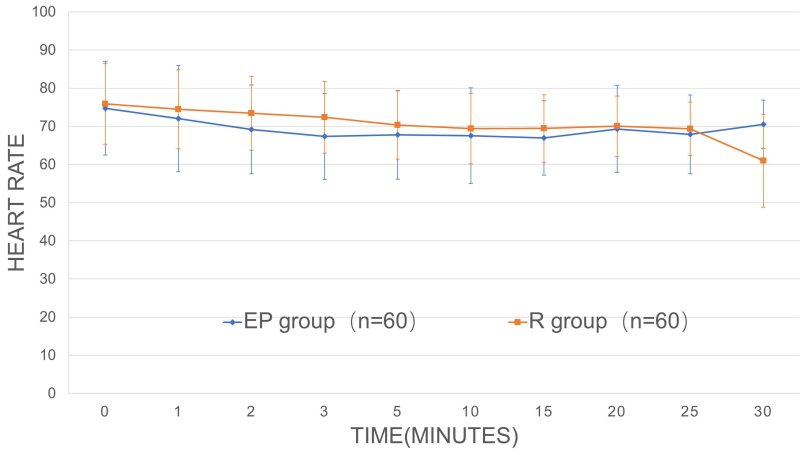

Figure 5 Comparison of heart rates. The heart rate of group R was higher than that of group EP at 2, 3 and 5 min after administration (P < 0.05).

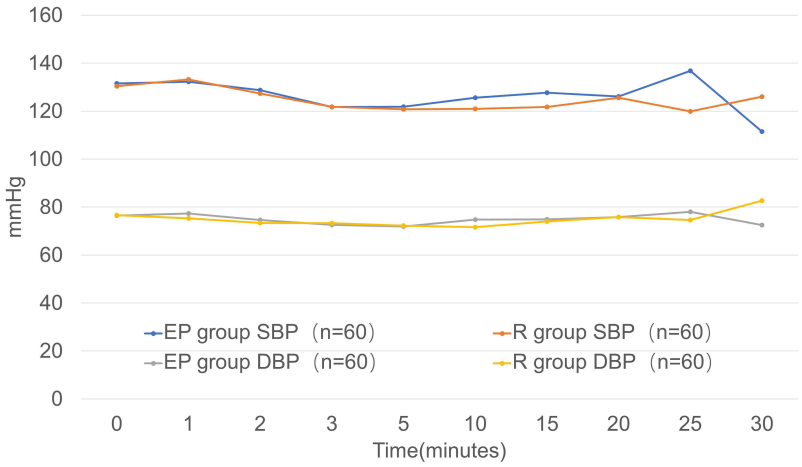

Figure 6 Comparison of blood pressure. Systolic blood pressure in EP group was higher than that in R group at 15 min and 25 min after administration ($P < 0.05$). There was no significant difference in diastolic blood pressure between the two groups ($P>0.05$).

For many years, propofol, midazolam, and etomidate have been the primary intravenous sedatives used in anesthesia practice; however, their respective advantages and disadvantages continue to pose challenges to anesthesiologists.[12,13] Propofol exhibits rapid onset, swift metabolism, and potent sedation depth; however, it is associated with injection pain and may lead to respiratory and circulatory depression. Deep anesthesia often causes respiratory and circulatory risks, especially in the elderly.[14–16] Therefore, in this study, the sedation level was maintained at mild-to-moderate (MOAA/S score ≤4) to evaluate whether remimazolam can be safely used in elderly patients. Etomidate is relatively more stable in breathing and circulation, but has the risk of muscle fibrillation and adrenal cortex suppression,[17] Although midazolam has minimal impact on respiration and circulation, its slow onset and prolonged metabolism can have a certain effect on patients' cognitive function.[18] To enhance the safety and optimize the benefits of various drugs, a combination of anesthetic agents is frequently employed to reduce the dosage of individual intravenous anesthetics, thereby minimizing complications while improving sedation efficacy and hastening recovery. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines on sedation and anesthesia for gastrointestinal endoscopy (2017 edition) recommend combining analgesia with sedation to achieve optimal outcomes.[19] Remifentanil, an ultra-short-acting opioid, was used for analgesia in this study. Remifentanil has rapid onset and metabolism, and is a commonly used analgesic drug in

Table 3 Comparison of Adverse Effects

	EP Group (n=60)	R Group (n=60)	Total (n=120)	P value
Hiccups (n, %)	0	8 (13.3%)	8 (6.7%)	0.003
Hypoxia (n, %)	3 (5.0%)	1 (1.7%)	4 (3.3%)	0.310
Depression of respiration (n, %)	6 (10.0%)	1 (1.7%)	7 (5.8%)	0.051
Tongue falling (n, %)	2 (3.3%)	1 (1.7%)	3 (2.5%)	0.559
Total respiratory-related adverse events (n, %)	11 (18.3%)	3 (5.0%)	14 (11.7%)	0.047
Choking cough (n, %)	0 (0.0%)	3 (5.0%)	3 (2.5%)	0.080
Movement of the body (n, %)	2 (3.3%)	1 (1.7%)	3 (2.5%)	0.559
Low blood pressure (n, %)	22 (36.7%)	24 (40%)	46 (38.33%)	0.851
Nausea (n, %)	1 (1.7%)	1 (1.7%)	2 (1.7%)	1
Dizziness (n, %)	1 (1.7%)	0 (0%)	1 (0.8%)	1

Table 4 Comparison of Follow-Up Questionnaires Before Discharge

Variate	Description Statistic	EP Group (n=60)	R Group (n=60)	P value
How was the sedation for your procedure?				<0.001
	Excellent	7 (11.7%)	40 (66.7%)	
	Good	43 (71.7%)	19 (31.7%)	
	Fair Poor	10 (16.7%)	1 (1.7%)	
Do you think you needed any adjustment of your sedation?				0.220
	Just right	58 (96.7%)	59 (98.3%)	
	Needed more	2 (3.3%)	0 (0.0%)	
	Needed less	0 (0.0%)	1 (1.7%)	
Do you remember the start of the procedure?				1
	No	57 (95.0%)	57 (95.0%)	
	Yes	3 (5.0%)	3 (5.0%)	
Do you remember being awake during the procedure?				0.662
	No	45 (75.0%)	48 (80.0%)	
	Yes	15 (25.0%)	12 (20.0%)	
Do you remember the end of the procedure when the instrument was removed?				1
	No	29 (48.3%)	30 (50.0%)	
	Yes	31 (57.7%)	30 (50.0%)	

Table 5 Comparison of Follow-Up Telephone Questionnaire 24-Hour After Procedure

Variate	Description Statistic	EP Group (n=59)	R Group (n=58)	P value
How was the sedation for your procedure?				<0.001
	Excellent	12 (20.3%)	37 (63.8%)	
	Good	39 (66.1%)	21 (36.2%)	
	Fair Poor	8 (13.6%)	0 (0.0%)	
Do you think you needed any adjustment of your sedation?				0.215
	Just right	54 (91.5%)	57 (98.3%)	
	Needed more	2 (3.4%)	0 (0.0%)	
	Needed less	3 (5.1%)	1 (1.7%)	
Do you remember the start of the procedure?				0.986
	No	57 (96.6%)	56 (96.6%)	
	Yes	2 (3.4%)	2 (3.4%)	

(*Continued*)

Table 5 (Continued).

Variate	Description Statistic	EP Group (n=59)	R Group (n=58)	P value
Do you remember being awake during the procedure?				0.479
	No	54 (91.5%)	55 (94.8%)	
	Yes	5 (8.5%)	3 (5.2%)	
Do you remember the end of the procedure when the instrument was removed?				0.008
	No	36 (61.0%)	49 (84.5%)	
	Yes	23 (39.0%)	9 (15.5%)	
Do you think that the rest of your day was impaired by the sedation?				0.027
	Severe	0	0	
	No	41 (69.5%)	51 (87.9%)	
	Yes	18 (30.5%)	7 (12.0%)	
Did you require additional sleep during the daytime after the procedure?				0.253
	No need or change from usual	50 (84.7%)	54 (93.1%)	
	Needed compared to the usual	9 (15.3%)	4 (6.9%)	

outpatient anesthesia. Currently, elderly patients are typically sedated with a combination of etomidate and propofol injections. Combination therapy can effectively reduce the dosage of a single drug, thereby mitigating associated adverse reactions.[20] Moreover, no apparent injection pain was observed, and its impact on respiration and circulation was minimal. Furthermore, this therapeutic approach has demonstrated rapid efficacy and facilitated prompt recovery,[21] this is why they were chosen as the control group in this study.

This study compared the sedative effects of remimazolam and etomidate combined with propofol. The results showed that in both groups, the MOAA/S score decreased quickly and decreased to a minimum at 3 min after administration, suggesting that remimazolam has same reliable sedative effect.[22,23] In the R group, the induction time was 1.5±0.63min, slightly longer but less than 2 min in both groups, and the MOAA/S score was higher in the first 2 min after administration. These results are similar to those found in a multicenter study by Wang et al[23] but recovery time was different, this may be related to the different trial protocols. The sedation success rates in the R and EP groups were 93.3% and 98.3%, respectively. Chen et al[24] confirmed that the sedation success rate of the R group was 97.35%, indicate remazolam had similar sedation success rates in older patients. The recovery times were 13.08±4.06 in R groups which was similar to that in Guo et al[25] elderly gastrointestinal endoscopy study, but the induction time was longer. The reason may be due to the different ways of medication, and the onset time is closely related to the amount of medication. Although deep anesthesia was not maintained in our study, in contrast, recovery times did not differ. The observation time in PACU of R group was shorter than that of EP group (15.17±2.46, 17.40±2.08) min, suggesting that remazolam is a rapid wake-up agent suitable for older outpatients and can speed up turnover. Although the difference is only 2 min, a saving of 20 min in the morning would be extremely significant since endoscopy sessions are all short (no more than 1 h).

Remimazolam is a new type of water-soluble ultrashort-acting anaesthetic sedative. Due to its special methyl propionate side chain mechanism, remimazolam showed a high clearance, a small steady-state volume of distribution and a short terminal half-life.[26] Based on reported clinical trials, remimazolam has demonstrated its promising properties,

including a rapid onset, a short duration of action, a predictable recovery profile, and metabolism almost unaffected by liver or renal function. As the depth of sedation increases, respiratory and circulatory systems tend to change. In both groups, the respiratory rate decreased from 1 to 5 min after the first administration, and then returned to baseline levels. The effect of EP on respiration was greater than that of remimazolam, and $PetCO_2$ decreased significantly at 1–10 min after administration decreased to the lowest value approximately 3 min after administration, and the respiratory rate was also lower than that of the R group. SpO_2 levels exhibited a slight decrease 3 min after administration in both groups; however, no statistically significant difference was observed at each time point. These findings suggest that remimazolam has a minimal impact on respiration.

The R group displayed higher heart rates than the EP group at first 5 minute post-administration suggest that remimazolam has a minimal impact on the heart rate and is more stable for use in elderly patients. The blood pressure of patients in both groups remained stable, with fluctuations between 110–140/75–85 mmHg and no need for drug treatment. Most studies have found stable blood pressure in the remimazolam group,[20] may be related to its enhances the dominance of sympathetic activity, leading to lower cardiopulmonary depression.[25] But in this study, a significant decrease in systolic blood pressure was observed mainly at 15 and 25 min after remimazolam administration, which may be attributed to the presence of remimazolam-induced hiccups. Continuous BP monitoring of blood pressure is recommended throughout the procedure when combined with remifentanil.

In terms of adverse reactions, the EP group exhibited significantly higher rates of respiratory-related events, such as hypoxia, respiratory depression, and tongue falling, than the R group, indicating remimazolam has superior safety profile and minimal impact on the respiratory system of elderly patients. However, the incidence of adverse hiccups was 13.3% higher in the remimazolam group than that in the EP group. Previous studies conducted by Liu et al[27] have demonstrated that midazolam administration significantly elevated the risk of hiccup development in patients undergoing endoscopy, with a statistically significant difference observed between the sedation and non-sedation groups (20.5% and 5.1%, respectively). Furthermore, patients with gastric reflux are more susceptible to developing hiccups. Hiccups may result in acute intrathoracic pressure changes, leading to hypotension and bradycardia owing to decreased vascular resistance caused by thoracic aortic dilation and increased volume. This may partially account for the reduction in systolic blood pressure observed in the 3–15 min R group after administration.[28] During anesthesia, hiccups can compromise respiratory function and pose a potential risk of pulmonary aspiration. Additionally, Vanner et al[29] found approximately 40% of patients experience hiccups and detectable gastroesophageal reflux after anesthesia induction. In our study, most hiccups occurred approximately three minutes after induction and persisted for one–three minutes. Although no aspiration events were observed, this remains a potential hazard, particularly in patients with compromised cardiac and pulmonary functions.

The questionnaire survey revealed that patients in the remimazolam group exhibited significantly higher satisfaction and amnesia levels than those in the EP group. Furthermore, 24-hour follow-up demonstrated that sedation did not affect the work or daily life of patients in the remimazolam group, nor was there a need for increased sleep time. Remimazolam have amnesia effect and no activity of metabolites which greatly improves the consciousness state of patients when they wake up. The comprehensive indicators such as reliable depth of sedation during sedation, rapid recovery of behavior and cognitive ability when awakening, less hangover, and no nausea and vomiting ultimately improve patient satisfaction. Some studies have shown that remimazolam is as beneficial as dexmedetomidine in reducing the incidence of POCD early after radical gastrectomy in elderly patients with gastric cancer, possibly due to a reduced inflammatory response.[30] The Postoperative cognitive function in elderly patients is a critical clinical concern. The Mini-Cog cognitive function score was selected because of its efficiency, convenience, high patient acceptance, and smooth screening process. Developed by Scanlan et al in 2000, the advantage of Mini-Cog lies in its ability to accurately assess cognitive function after short-term training, without being influenced by educational or cultural factors. Additionally, it is highly efficient and inexpensive, making it an ideal tool for assessing patients with cognitive impairment.[10,31] This study revealed that patients in the R group exhibited higher scores than those in the EP group, indicating that remimazolam has less of an impact on postoperative cognitive function and is a safer option for elderly patients.

This single center prospective randomized controlled trial compared the efficacy and adverse effects of remimazolam tosilate with those of the commonly used sedatives in clinical practice. The results indicate that the administration of

remimazolam and remifentanil can provide safe and effective sedation and analgesia options for elderly patients undergoing gastrointestinal endoscopy. It confers numerous benefits including stable respiration and hemodynamics, consistent sedation, minimal impact on cognitive function, and high levels of patient satisfaction. However, this study has some limitations. First, the incidence of hiccups in the remimazolam group was higher, which has only been observed clinically and has not yet been explored using laboratory molecular biology. In addition, the specific mechanisms underlying this observation remain unclear. The cases included in the study were from a single center, and potential selection bias could not be ruled out. In future research, a multicenter clinical analysis will be conducted to further validate our findings. This preliminary exploration of cognitive function warrants more comprehensive investigation and research programs that integrate laboratory test data and molecular mechanism Discussions to elucidate our results.

Conclusion

Remimazolam besylate for sedation of the ASA I-II elderly population for the gastroscopy procedure are non-inferior to etomidate combined with propofol, however, care should be taken to monitor some adverse effects such as hiccups.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Peking University People's Hospital (2021PHB002-001).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Behrens A, Kreuzmayr A, Manner H, et al. Acute sedation-associated complications in GI endoscopy (ProSed 2 Study): results from the prospective multicentre electronic registry of sedation-associated complications. *Gut*. 2019;68(3):445–452. doi:10.1136/gutjnl-2015-311037
2. Patel S, Vargo JJ, Khandwala F, et al. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol*. 2005;100(12):2689–2695. doi:10.1111/j.1572-0241.2005.00320.x
3. Frieling T, Heise J, Kreysel C, Kuhlen R, Schepke M. Sedation-associated complications in endoscopy--prospective multicentre survey of 191142 patients. *Z Gastroenterol*. 2013;51(6):568–572. doi:10.1055/s-0032-1330441
4. Patterson KW, Casey PB, Murray JP, O'Boyle CA, Cunningham AJ. Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *Br J Anaesth*. 1991;67(1):108–111. doi:10.1093/bja/67.1.108
5. Stohr 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
6. Choi JY, Lee HS, Kim JY, et al. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: a randomized non-inferiority trial. *J Clin Anesth*. 2022;82:110955. doi:10.1016/j.jclinane.2022.110955
7. Lee A, Shirley M. Remimazolam: a review in procedural sedation. *Drugs*. 2021;81(10):1193–1201. doi:10.1007/s40265-021-01544-8
8. Chen L, Liang X, Tan X, Wen H, Jiang J, Li Y. Safety and efficacy of combined use of propofol and etomidate for sedation during gastroscopy: systematic review and meta-analysis. *Medicine*. 2019;98(20):e15712. doi:10.1097/MD.0000000000015712
9. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10(4):244–251.
10. Trongsakul S, Lambert R, Clark A, Wongpakaran N, Cross J. Development of the Thai version of Mini-Cog, a brief cognitive screening test. *Geriatr Gerontol Int*. 2015;15(5):594–600. doi:10.1111/ggi.12318
11. Borkett KM, Riff DS, Schwartz HI, et al. A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056) versus midazolam for sedation in upper gastrointestinal endoscopy. *Anesth Analg*. 2015;120(4):771–780. doi:10.1213/ane.0000000000000548
12. Leslie K, Allen ML, Hessian EC, et al. Safety of sedation for gastrointestinal endoscopy in a group of university-affiliated hospitals: a prospective cohort study. *Br J Anaesth*. 2017;118(1):90–99. doi:10.1093/bja/aew393
13. Wang Y, Xu H, Li H, et al. Postoperative complications associated with moderate sedation in endoscopic procedures among patients with cirrhosis. *Med Sci Monit*. 2021;27:e933082. doi:10.12659/msm.933082
14. Tekeli AE, Oguz AK, Tuncdemir YE, Almali N. Comparison of dexmedetomidine-propofol and ketamine-propofol administration during sedation-guided upper gastrointestinal system endoscopy. *Medicine*. 2020;99(49):e23317. doi:10.1097/MD.0000000000023317
15. Lee JS, Kim ES, Cho KB, Park KS, Lee YJ, Lee JY. Pain intensity at injection site during esophagogastroduodenoscopy using long- and medium-chain versus long-chain triglyceride propofol: a randomized controlled double-blind study. *Gut Liver*. 2021;15(4):562–568. doi:10.5009/gnl20243

16. Sneyd JR, Absalom AR, Barends CRM, Jones JB. Hypotension during propofol sedation for colonoscopy: a retrospective exploratory analysis and meta-analysis. *Br J Anaesth*. 2022;128(4):610–622. doi:10.1016/j.bja.2021.10.044
17. Kim MG, Park SW, Kim JH, et al. Etomidate versus propofol sedation for complex upper endoscopic procedures: a prospective double-blinded randomized controlled trial. *Gastrointest Endosc*. 2017;86(3):452–461. doi:10.1016/j.gie.2017.02.033
18. Zhang L, Li C, Zhao C, You Y, Xu J. The comparison of remimazolam and midazolam for the sedation of gastrointestinal endoscopy: a meta-analysis of randomized controlled studies. *Afr Health Sci*. 2022;22(2):384–391. doi:10.4314/ahs.v22i2.44
19. Early DS, Lightdale JR, Vargo JJ, et al.; Committee ASoP. Guidelines for sedation and anesthesia in GI endoscopy. *Gastrointest Endosc*. 2018;87(2):327–337. doi:10.1016/j.gie.2017.07.018
20. Shen XC, Ao X, Cao Y, et al. Etomidate-remifentanil is more suitable for monitored anesthesia care during gastroscopy in older patients than propofol-remifentanil. *Med Sci Monit*. 2015;21:1–8. doi:10.12659/msm.891183
21. Meng QT, Cao C, Liu HM, et al. Safety and efficacy of etomidate and propofol anesthesia in elderly patients undergoing gastroscopy: a double-blind randomized clinical study. *Exp Ther Med*. 2016;12(3):1515–1524. doi:10.3892/etm.2016.3475
22. Chae D, Kim HC, Song Y, Choi YS, Han DW. Pharmacodynamic analysis of intravenous bolus remimazolam for loss of consciousness in patients undergoing general anaesthesia: a randomised, prospective, double-blind study. *Br J Anaesth*. 2022;129(1):49–57. doi:10.1016/j.bja.2022.02.040
23. Wang X, Hu X, Bai N, et al. Safety and efficacy of remimazolam besylate in patients undergoing colonoscopy: a multicentre, single-blind, randomized, controlled, phase III trial. *Front Pharmacol*. 2022;13:900723. doi:10.3389/fphar.2022.900723
24. Chen SH, Yuan TM, Zhang J, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: a multicenter, randomized, non-inferiority, Phase III trial. *J Gastroenterol Hepatol*. 2021;36(2):474–481. doi:10.1111/jgh.15188
25. Guo J, Qian Y, Zhang X, Han S, Shi Q, Xu J. Remimazolam tosilate compared with propofol for gastrointestinal endoscopy in elderly patients: a prospective, randomized and controlled study. *BMC Anesthesiol*. 2022;22(1):180. doi:10.1186/s12871-022-01713-6
26. Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: pharmacologic considerations and clinical role in anesthesiology. *Pharmacotherapy*. 2016;36(9):1021–1027. doi:10.1002/phar.1806
27. Liu CC, Lu CY, Changchien CF, Liu PH, Perng DS. Sedation-associated hiccups in adults undergoing gastrointestinal endoscopy and colonoscopy. *World J Gastroenterol*. 2012;18(27):3595–3601. doi:10.3748/wjg.v18.i27.3595
28. Mathew OP. Effects of transient intrathoracic pressure changes (hiccups) on systemic arterial pressure. *J Appl Physiol*. 1997;83(2):371–375. doi:10.1152/jappl.1997.83.2.371
29. Vanner RG. Gastro-oesophageal reflux and hiccup during anaesthesia. *Anaesthesia*. 1993;48(1):92–93. doi:10.1111/j.1365-2044.1993.tb06830.x
30. Liao YQ, Min J, Wu ZX, Hu Z. Comparison of the effects of remimazolam and dexmedetomidine on early postoperative cognitive function in elderly patients with gastric cancer. *Front Aging Neurosci*. 2023;15:1123089. doi:10.3389/fnagi.2023.1123089
31. Lourenco RA, Filho Ribeiro ST. The accuracy of the Mini-Cog in screening low-educated elderly for dementia. *J Am Geriatr Soc*. 2006;54(2):376–377; authorreply 377–378. doi:10.1111/j.1532-5415.2005.00592_8_1.x