

ED50 and ED95 of Remimazolam Tosilate Combined with Different Doses of Fentanyl in Elderly Patients for Painless Gastroscopy

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Background: The novel short-acting benzodiazepine drug, remimazolam tosilate, has been employed for sedation during endoscopic procedures. The optimal loading dosage of remimazolam tosilate in gastroscopy for elderly patients when co-administered with fentanyl remains unclear. Therefore, the primary objective of our research was to ascertain the median effective dose (ED50) and the 95% effective dose (ED95) of remimazolam tosilate in combination with various fentanyl dosages for elderly patients undergoing painless gastroscopy.

Methods: Seventy-five patients aged ≥ 65 years and American Society of Anesthesiologists (ASA) class I–III were recruited to undergo elective painless gastroscopy. All patients were randomized assigned to group F₁, group F₂, and group F₃, and were injected intravenously with different doses of fentanyl (0.5 ug/kg, 1 ug/kg, and 1.5 ug/kg) 3 minutes prior to the administration of remimazolam tosilate, respectively. The initial preset dose of remimazolam tosilate was 0.3 mg/kg in group F₁, 0.2 mg/kg in group F₂, 0.15 mg/kg in group F₃. The dose gradient was 0.02 mg/kg per group according to the up-and-down sequential method. Probit regression model was employed to determine the ED50 and ED95 of remimazolam tosilate.

Results: The ED50 of remimazolam tosilate in group F₃ was lower than that in group F₁ and F₂ (0.095 [0.088–0.108] mg/kg vs 0.162 [0.153–0.171] mg/kg; 0.258 [0.249–0.266] mg/kg, $p < 0.05$). The ED95 of remimazolam tosilate was 0.272 mg/kg (95% CI: 0.264–0.295 mg/kg) in group F₁, 0.175 mg/kg (95% CI: 0.167–0.200 mg/kg) in group F₂ and 0.109 mg/kg (95% CI: 0.101–0.135 mg/kg) in group F₃. The total dosage of remimazolam tosilate decreased gradually with the increasing of fentanyl ($p < 0.001$). The frequency of injection pain was higher in group F₁ compared to groups F₂ and F₃ ($p < 0.05$). The patients in group F₃ had a lower incidence of hypotension than in groups F₁ and F₂ ($p < 0.05$). There was no respiratory depression, intraoperative consciousness, dizziness or delirium in the three groups.

Conclusion: The concurrent use of fentanyl reduces the dosage of remimazolam tosilate required for sedative gastroscopy in elderly patients in a dose-dependent manner. Moreover, 1.5 ug/kg fentanyl combined with remimazolam tosilate may reduce the incidence of hypotension and injection pain. These findings should be confirmed in a large-scale study.

Keywords: painless gastroscopy, elderly patients, median effective dose, fentanyl, remimazolam tosilate

Introduction

The use of gastrointestinal endoscopy is considered the gold standard for both diagnosing and treating upper gastrointestinal diseases.¹ The number of elderly adults undergoing gastroscopy is increasing yearly due to the aging population and advancements in gastrointestinal endoscopy technology.² Procedural sedation during gastroscopy can alleviate patients' pain, anxiety, vomit, and discomfort.³ Although procedural sedation is considered safe in the majority of patients, elderly patients who receive procedural sedation have an increased risk of respiratory depression,⁴ hemodynamic instability,⁵ arrhythmias,⁶ and delayed discharge⁷ due to the use of certain sedative agents, such as propofol. Therefore, it is crucial for clinicians to select safe and efficient medications for gastroscopy in elderly patients. However, the use of sedative medications in elderly patients during gastroscopy remains controversial.

The newly developed remimazolam tosylate is a short-acting agonist of the gamma-aminobutyric acid A (GABA) receptor, which effectively inhibits neuronal electrical activity by binding to GABA receptors and induces sedation.^{8,9} It is rapidly hydrolyzed by hepatic esterases to inactive carboxylic acid metabolites.¹⁰ In comparison to conventional benzodiazepine sedative medications, remimazolam tosylate has a quicker onset and elimination, milder respiratory and circulatory depression, and fewer adverse effects.^{11–13} The safety and efficacy of remimazolam tosylate as a medication for procedural sedation in elderly patients have been demonstrated by several studies.^{14–16} Borkett et al found that a single administration of remimazolam tosylate given at 0.1–0.2 mg/kg has a high sedation success rate with minimal effects on breathing and circulation during upper gastrointestinal endoscopy. However, the procedure success rate have ranged from 32% to 64%.¹⁷ In clinical practice, we also found that the above dose of remimazolam tosylate may be insufficient for achieving adequate sedation in certain patients during gastroscopy, with a higher incidence of cough, hiccup, body movement, which could potentially be attributed to the weak inhibitory effect of remimazolam tosylate on the stress response. Although increasing the dose of remimazolam tosylate can improve the depth of sedation and suppress the stress response, it has a significant inhibitory effect on the patient's circulatory system, prolonging the time to awaken and leave the hospital. So, for gastroscopy sedation, drug combinations may be preferable to single-drug regimen.¹⁸ Hu et al demonstrated that a combination of 0.1 ug/kg sufentanil and 0.2 mg/kg remimazolam tosylate effectively provided sufficient sedation for elderly patients undergoing gastroscopy.¹⁹ Guo et al also revealed that 5 ug/kg alfentanil in combination with 0.15 mg/kg remimazolam tosylate can be safely and effectively used for sedation during gastrointestinal endoscopy in elderly patients,²⁰ which may be attributed to the fact that opioids provide better analgesia and reduce the amount of intraoperative sedative medication.^{21,22} However, the ED50 of remimazolam tosylate combined with different doses of fentanyl in elderly patients for painless gastroscopy has not been completely evaluated. Therefore, the objective of this study was to ascertain the optimal and efficacious dosage of remimazolam tosylate in combination with varying doses of fentanyl for painless gastroscopy in elderly patients.

Materials and Methods

Ethics Approval

The study received approval from the Ethics Committee of Affiliated Hospital of North Sichuan Medical College, Nanchong, China (Approval No. 2023ER368-1) and was registered on the Chinese Clinical Trials Registry at <http://www.chictr.org.cn> (ChiCTR2300077778). The study was commenced after obtaining written informed consent from all participants.

Study Population

The study recruited a total of 75 patients aged ≥ 65 years, who met the American Society of Anesthesiologists (ASA) physical status I–III, for painless gastroscopy from November 2023 to January 2024.

The exclusion criteria were as follows: patients who declined to sign written informed consent; uncontrolled severe hypertension; experienced significant cardiorespiratory instability, including acute heart failure, myocardial infarction, acute respiratory infection; patients who had a history of alcohol abuse or dependence on opioids or benzodiazepines; Additionally, patients who had a documented allergy or medical contraindication to benzodiazepines or opioids.

Randomization and Blinding

75 patients were randomised into three groups: group F₁ with a dose of 0.5ug/kg fentanyl, group F₂ with a dose of 1 ug/kg fentanyl and group F₃ with a dose of 1.5ug/kg fentanyl. The randomization process was conducted utilizing a computer-generated randomized sequence. The study medication was prepared on the day of endoscopy by an independent anaesthesia nurse according to the randomization sequence. Prior to gastroscopy, the fentanyl dose for each patient was diluted to 5 mL with 0.9% saline using the same syringe. Different doses of remimazolam tosylate were diluted to 20 mL with 0.9% saline in identical syringes. All patients, endoscopist, and other investigators were masked to group allocation.

Anaesthesia

All patients underwent an 8-hour fasting period and were prohibited from consuming water for two hours prior to the procedure. In the operating room, all patients were positioned on the left side with lower limb flexion. Peripheral venous

access was established in the left upper limb. Vital signs, including blood pressure, heart rate and pulse oxygen saturation (SpO₂) were monitored, and oxygen was supplied via the nasal catheter at a flow rate of 5 L/min before giving intravenous drugs. Fentanyl was given intravenously. After about three minutes following the administration of fentanyl, remimazolam tosilate was injected slowly within 1 min. Gastroscopy was inserted after the patient lost consciousness (Modified Observer's Assessment of Alertness/Sedation Scale, MOAA/S score \geq 1). The patient's level of sedation was evaluated using the MOAA/S score (score 5: prompt response to the spoken name in a normal tone; score 4: sluggish response to the spoken name in a normal tone; score 3: responds only after the name is called loudly and/or repeatedly; score 2: responds only after mild prodding or shaking; score 1: responds only after experiencing painful trapezius squeeze; score of 0: no response even after painful trapezius squeeze). Remimazolam tosilate 3 mg administered intravenously for therapeutic sedation if the patient presented out coughing, swallowing, retching, frowning, body movement during gastroscopy. After the procedures, patients with MOAA/S score \geq 4 were sent to the recovery room for observation, and were accompanied by their family members to leave the hospital after the Modified Aldrete score \geq 9.²³ The definition of perioperative hypotension was SBP below 90 mmHg or Mean arterial pressure (MAP) decreased by more than 20% of the baseline value, and ephedrine 6 mg was administered. Bradycardia was defined if heart rate (HR) below 50 beats/min, and atropine 0.3 mg was given. The lower jaw was elevated if hypoxemia (SpO₂ < 95%) occurred. If the SpO₂ did not increase or continued to fall below 90%, mask-assisted ventilation was carried out.

Determination of the ED50 for Remimazolam Tosilate

The median effective dose of remimazolam tosilate, when combined with different doses of fentanyl for each group, was determined utilizing the up-and-down sequential methodology. The initial dosage of remimazolam tosilate (0.3 mg/kg in group F₁, 0.2 mg/kg in group F₂, 0.15 mg/kg in group F₃) was determined by the pretest data. The subsequent patient's dose of remimazolam tosilate would be increased by 0.02 mg/kg if the previous patient exhibited a positive response to gastroscopy placement. The subsequent patient's remimazolam tosilate dose would be reduced by 0.02 mg/kg if the previous patient exhibited a negative response to gastroscopy placement. Positive response to gastroscopy placement was defined as the patient presenting out coughing, swallowing, retching, frowning, body movement. The absence of the above behavior was considered a negative reaction. A cross-over point was defined as a situation where there is a switch from a positive response to a negative response, or vice versa, in consecutive patients. When six cross-over points were obtained in each group, we considered that the sample size for this study was adequate.

Secondary Data Collection

We monitored SBP, diastolic blood pressure (DBP), SPO₂, HR and MAP at the following time points: before the administration of fentanyl (T₀), insertion of the endoscope into the pharyngeal cavity (T₁), withdrawal of the endoscope from the pharyngeal cavity (T₂), the time of awakening from anesthesia (T₃), the time away from the recovery room (T₄). The procedure time, consciousness recovery time, length of recovery room stay, and adverse effects, including injection pain, hypotension, bradycardia, respiratory depression, were documented. In the postanesthesia care unit, intraoperative awareness, postoperative dizziness, postoperative delirium and postoperative nausea and vomiting, were assessed and documented.

Statistical Analysis

Statistical analysis was conducted using SPSS 25.0 software. The Shapiro–Wilk test was utilized to assess the normality of the data. The continuous distributed variables were reported as mean \pm standard deviation (SD) or median (25th to 75th percentiles), where appropriate, and were analyzed using one-way ANOVA or the non-parametric Kruskal–Wallis *H*-test. The categorical data were quantified as numerical values (expressed as percentages) and subjected to analysis using the chi-square test.

Comparisons between groups were made using the Bonferroni test. $P < 0.05$ was considered statistically significant. Probit probability unit regression analysis was employed to determine ED₅₀, ED₉₅ and the 95% confidence interval (CI) of remimazolam tosilate. The comparison of ED₅₀ for each group used by relative median intensity.

Results

The study recruited a total of 75 patients, with each group consisting of 25 patients. 7, 8, 9 patients in groups F₁, F₂ and F₃ were excluded from the study because six crossover points were achieved in each group (Figure 1). The study was completed by 18, 17, and 16 patients in groups F₁, F₂, and F₃ respectively. The demographic characteristics did not show any significant differences among the three groups (Table 1).

The sequential doses of remimazolam tosilate in combination with fentanyl using up-and-down sequential method are illustrated in Figure 2. The ED₅₀ and ED₉₅ of remimazolam tosilate is 0.258 mg/kg (95% CI: 0.249–0.266 mg/kg) and 0.272 mg/kg (95% CI: 0.264–0.295 mg/kg) in group F₁, 0.162 mg/kg (95% CI: 0.153–0.171 mg/kg) and 0.175 mg/kg (95% CI: 0.167–0.200 mg/kg) in group F₂, 0.095 mg/kg (95% CI: 0.088–0.108 mg/kg) and 0.109 mg/kg (95% CI: 0.101–0.135 mg/kg) in group F₃ (Table 2).

The SBP, DBP, MAP, and HR values did not exhibit any statistically differences among the three groups at various time points (Table 3). The total dosage of remimazolam tosilate demonstrated a significant negative correlation with the dosage of fentanyl ($p < 0.001$). The incidence of injection pain was significantly higher in patients in group F₁ than in

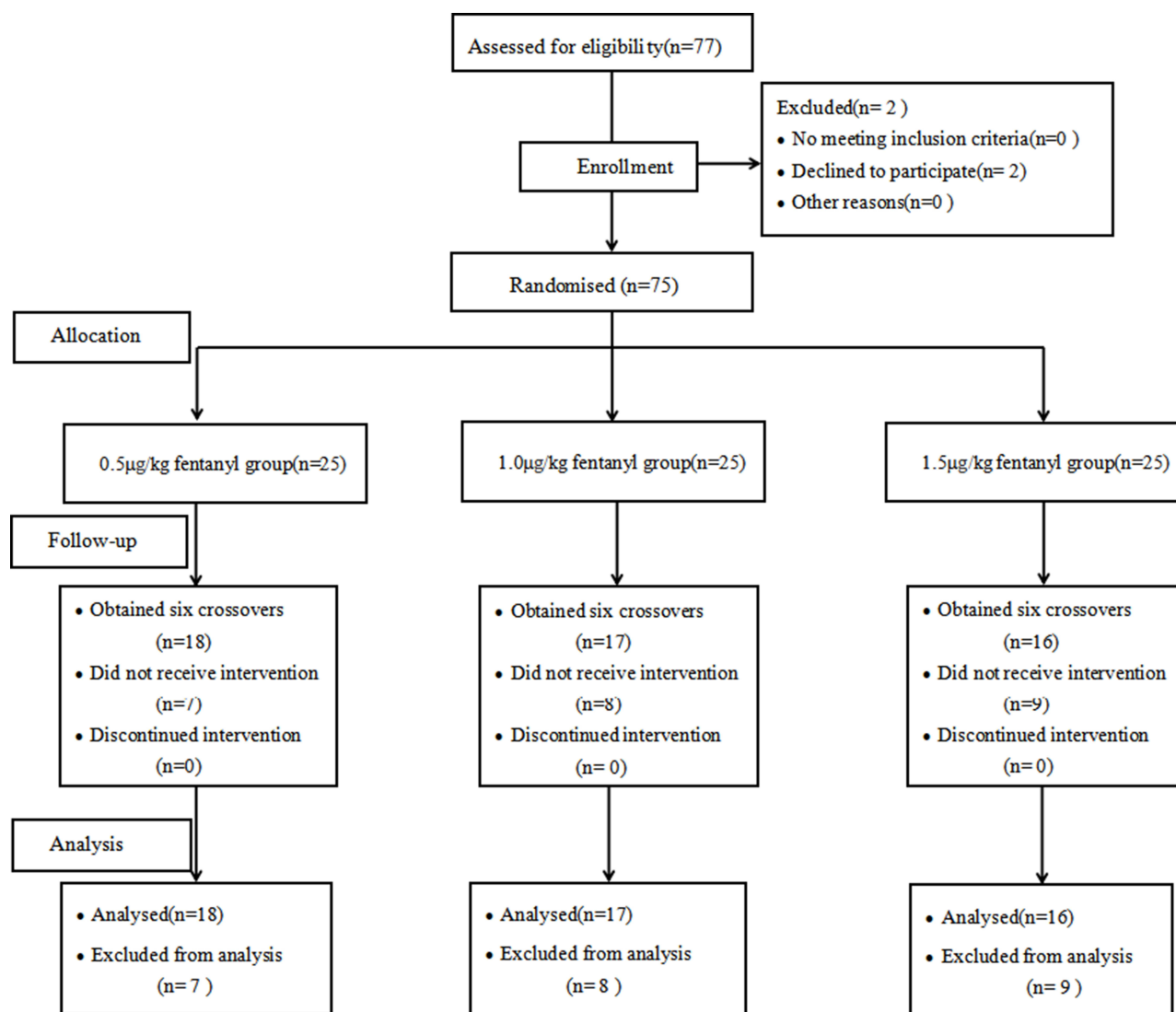


Figure 1 CONSORT flow diagram.

Abbreviation: CONSORT, Consolidated Standards of Reporting Trials.

Table I Demographic Characteristics for Three Groups

	Group F ₁ (n=18)	Group F ₂ (n=17)	Group F ₃ (n=16)	P value
Age(y)	71.28±3.10	71.65±4.03	72.13±2.94	0.112
Sex (M/F)	10/8	11/6	8/8	0.689
Height(cm)	159.28±6.59	158.24±10.35	159.56±8.26	0.516
Weight(kg)	61.39±7.19	58.06±8.56	60.06±8.98	0.657
BMI (kg/m ²)	24.21±2.66	23.49±5.48	23.58±2.99	0.679
ASA (II/III)	15/3	14/3	14/2	0.876

Notes: Data are presented as the mean ± SD or as the number of patients, as appropriate.

Abbreviations: M, male; F, female; BMI, body mass index; ASA, American Society of Anesthesiologists.

groups F₂ and F₃. No statistically difference between groups F₂ and F₃. There was no statistically difference in the incidence of hypotension between patients in groups F₁ and F₂. While patients in group F₃ had a considerably lower incidence of hypotension than in groups F₁ and F₂. The three groups did not differ in duration of gastroscopy, time of consciousness recovery, length of recovery room stay, incidence of hiccup. No respiratory depression, intraoperative awareness, postoperative nausea and vomiting, postoperative dizziness, or delirium was observed in either group (Table 4).

Discussion

In our study, we found that the ED₅₀ of remimazolam tosilate in combination with fentanyl are 0.258 mg/kg (with a dosage of 0.5 ug/kg fentanyl) and 0.162 mg/kg (with a dosage of 1.0 ug/kg fentanyl), 0.095 mg/kg (with a dosage of 1.5 ug/kg fentanyl), respectively. The administration of intravenous fentanyl results in a dose-dependent decrease in the ED₅₀ of remimazolam tosilate undergoing painless gastroscopy in elderly patients. It is suggested that fentanyl and remimazolam tosilate have a strong synergistic effect, and this synergistic effect can reduce the dose of sedatives and the risk of hypotension and injection pain, consistent with Kops study.²⁴ Tan et al found that when combined with a dosage of 0.1ug/kg sufentanil, the ED₅₀ of remimazolam besylate in the procedural sedation was 0.196 mg/kg during endoscopic retrograde cholangiopancreatography (ERCP).²⁵ These results are larger than the ED₅₀ of remimazolam tosilate combined with 1 ug/kg fentanyl in our study, which may be attributed the milder stimulation of gastroscopy compared with ERCP.²⁶ Another reason is that elderly patients exhibit heightened sensitivity to sedative drugs and opioids.²⁷ Cao et al observed that ED₅₀ of remimazolam tosilate was 0.097 mg/kg in combination with 0.15 ug/kg sufentanil for sedation in patients aged from 18–65 years old undergoing oesophagogastric varices screening endoscopy with liver cirrhosis.²⁸ The results are similar to our study. However, considering the potential impact of both age and liver function on drug sensitivity. Future studies will focus on investigating the optimal dosage of remimazolam tosilate in combination with opioids for painless gastroscopy in elderly patients with cirrhosis.

There are 27.7% patients in the F₁ group who experienced injection pain. The injection pain of remimazolam tosilate was significantly reduced compared with propofol,²⁹ which can be attributed to the water-solubility of remimazolam tosilate, and consequently, there is less injection pain than fat-soluble agents. However, the mechanism of injection pain caused by remimazolam tosilate in our study remains unclear and needs further study. Fortunately, we also found that the administration of 1 ug/kg or 1.5 ug/kg fentanyl significantly reduced the occurrence of injection pain, which may be due to the appropriate dose of opioid preconditioning³⁰ and lower doses of remimazolam tosilate.²⁷ The incidence of hypotension gradually decreased with increasing doses of fentanyl in our study, which may be attributed to a reduction in remimazolam tosilate doses. Dai et al have shown that the hypotension incidence increased with higher doses of remimazolam tosilate.³¹

Our investigation demonstrated that the rates of intraoperative hiccups were 33.3% in group F₁, 23.5% in group F₂, and 18.7% in group F₃. The incidence of hiccups showed a decreasing trend although there was no clinical significance among

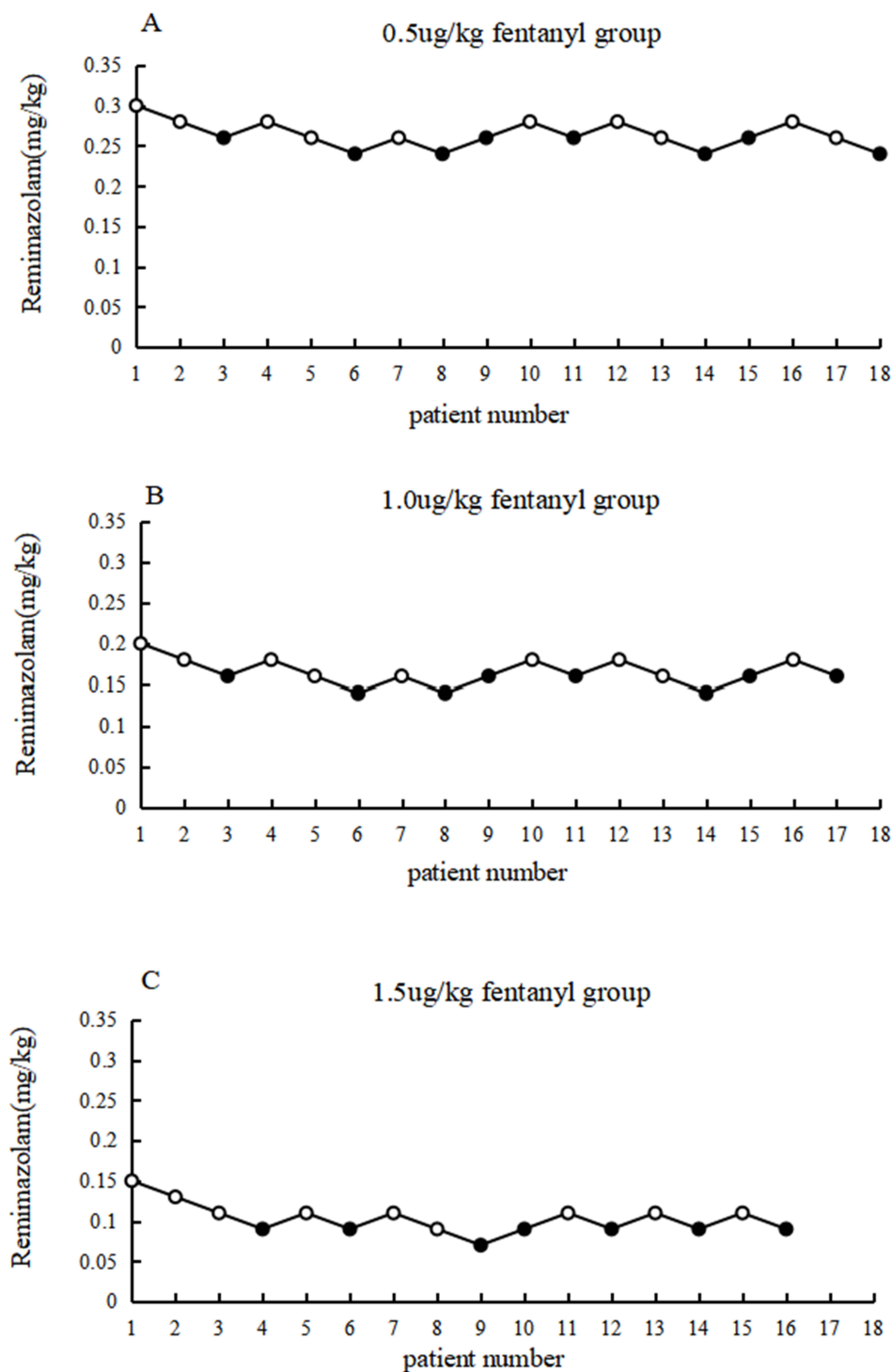


Figure 2 Individual response to the stimulus of gastroscopy placement in the study groups. Positive response to gastroscopy placement are marked with ●, and negative reaction to gastroscopy placement are marked with ○. The doses of fentanyl in group F₁ were 0.5ug/kg (A), in group F₂ were 1.0ug/kg (B), in group F₃ were 1.5 μg/kg (C), respectively. To get six crossovers, 18, 17 and 16 patients were included individually in groups F₁, F₂, F₃.

three groups. According to Liu et al, midazolam was also found to be strongly linked to an increased risk of hiccups.³² Additionally, they discovered that individuals who were given 2 mg of midazolam experienced hiccups more frequently than those who were given 1 mg. Davis et al thought that the hiccups may be due to the effect of benzodiazepines on the supraspinal hiccup centers located in the brainstem.³³ Another factor causing benzodiazepines-induced hiccups could be a direct

Table 2 ED50 and ED95 of Remimazolam Tosilate and Its 95% CI for the Three Groups

	Group F ₁ (n=18)	Group F ₂ (n=17)	Group F ₃ (n=16)
ED50 (mg/kg)	0.258 (0.249–0.266)	0.162 (0.153–0.171) ^a	0.095 (0.088–0.108) ^{ab}
ED95 (mg/kg)	0.272 (0.264–0.295)	0.175 (0.167–0.200)	0.109 (0.101–0.135)

Notes: ^aP < 0.05 versus Group F₁. ^bP < 0.05 versus Group F₂.

Abbreviations: ED50, median effective dose; ED95, 95% effective dose; CI, confidence intervals.

Table 3 SBP, DBP, HR, SPO2 at Different Time Points for Three Groups

	Group F ₁ (n=18)	Group F ₂ (n=17)	Group F ₃ (n=16)	P value
SBP (mmHg)				
T ₀	120.24±10.33	126.45±13.34	121.52±15.73	0.329
T ₁	105.92±11.34	112.71±13.92	118.54±14.23	0.119
T ₂	97.25±7.86	101.63±10.34	100.82±8.64	0.227
T ₃	99.72±7.43	101.52±10.34	99.72±9.04	0.949
T ₄	100.73±10.45	104.72±12.74	106.92±13.91	0.372
DBP (mmHg)				
T ₀	72.72±11.63	66.05±10.92	69.51±11.62	0.226
T ₁	62.32±12.13	61.33±11.94	69.14±11.42	0.161
T ₂	56.83±7.04	56.35±4.57	61.83±9.85	0.082
T ₃	59.14±9.15	55.65±8.36	62.14±8.65	0.112
T ₄	66.82±9.74	63.25±9.36	65.45±10.35	0.257
MAP (mmHg)				
T ₀	87.25±8.77	84.55±10.71	86.75±10.29	0.714
T ₁	76.27±12.48	77.72±11.44	85.51±13.72	0.082
T ₂	69.27±6.55	70.72±7.13	79.93±12.94	0.082
T ₃	71.33±6.05	70.14±8.62	74.28±7.33	0.173
T ₄	75.33±7.84	78.52±10.54	80.62±11.43	0.576
HR (bpm)				
T ₀	74.12±10.03	73.45±7.52	75.82±12.23	0.776
T ₁	70.72±9.33	72.24±8.82	76.14±11.82	0.283
T ₂	74.32±8.04	70.23±9.05	69.52±12.75	0.965
T ₃	77.25±8.44	69.73±9.64	70.12±11.93	0.962
T ₄	70.52±8.43	71.52±6.93	73.24±9.22	0.368

Notes: Data are presented as mean ± SD or number. Significance for post hoc analysis after analysis of variance (ANOVA) was corrected with Bonferroni's method. T₀ is the time before the administration of fentanyl, T₁ is the time when the endoscope was inserted into the pharyngeal cavity, T₂ is the time when the endoscope was pulled out of the pharyngeal cavity, and T₃ is the time of awakening from anesthesia. T₄ is the time away from recovery room.

Abbreviations: SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, Average arterial blood pressure; HR, heart rate.

stimulation of the diaphragm contractility.³⁴ In our study, complications such as reflux aspiration and gastric injury did not increase in patients with hiccups during gastroscopy, nor did they affect the doctor's operation of gastroscopy. However, according to Vanner's study, about 40% of patients with hiccups after induction of anesthesia have detectable gastroesophageal reflux.³⁵ So, in future study, we will focus on how to prevent or inhibit the adverse reactions of remimazolam tosylate - induced hiccups.

The present study has several potential limitations. Firstly, we utilize the MOAA/S score as a means of assessing the level of sedation depth in all patients. However, due to the absence of objective monitoring techniques such as bispectral indices or narcotrend, this approach may introduce potential biases into the evaluation process of sedation. Secondly, our study only

Table 4 Intraoperative and Postoperative Data

	Group F ₁ (n=18)	Group F ₂ (n=17)	Group F ₃ (n=16)	P value
Total dosage of remimazolam tosilate (mg)	17.46 ± 1.85	11.23 ± 1.49 ^a	7.51 ± 1.73 ^{ab}	<0.001
Duration of Gastroscopy(min)	7.25 (7.00–8.10)	8.0 (7.00–8.20)	8.75 (8.00–9.00)	0.056
Time of consciousness recovery (min)	6.33 ± 1.74	5.94 ± 2.10	5.75 ± 1.48	0.629
Length of recovery room stay (min)	31.11 ± 9.57	30.25 ± 9.16	30.04 ± 7.53	0.751
Hypoxemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.0
Injection pain	5 (27.78%)	1 (5.88%) ^a	0 (0.00%) ^a	0.038
Hiccup	7 (38.89%)	4 (23.53%)	3 (18.75%)	0.423
Hypotension	6 (33.33%)	4 (23.53%)	0 (0.00%) ^a	0.037
Bradycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.0
Intraoperative awareness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.0
Postoperative nausea and vomiting	2 (11.11%)	1 (5.88%)	1 (5.88%)	1.0
Postoperative delirium	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.0
Postoperative dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1.0

Notes: Data are presented as the mean ± SD, median (25th to 75th percentiles) or as the number (proportion) as appropriate. ^aP < 0.05 versus Group F₁. ^bP < 0.05 versus Group F₂.

includes elderly patients with a normal BMI, thus limiting the generalizability of our findings to other patients. Thirdly, this study is a single-center design and small sample size. Therefore, the subsequent trials necessitate a larger sample size and multi-centre studies to further investigate the adverse effects and recovery time of different dose of fentanyl in combination with varying appropriate doses of remimazolam tosilate in painless gastroscopy for elderly patients.

Conclusion

The administration of fentanyl results in a dose-dependent reduction in the ED₅₀ of remimazolam tosilate undergoing painless gastroscopy in elderly patients. Moreover, the administration of 1.5 ug/kg fentanyl resulted in a reduction in the occurrence of hypotension and injection pain.

Abbreviations

ED₅₀, median effective dose; ED₉₅, the 95% effective dose; ASA, American Society of Anesthesiologists; GABA_A, gamma-aminobutyric acid A; SpO₂, pulse oxygen saturation; MOAA/S score, Modified Observer's Assessment of Alertness/Sedation Scale; SBP, Systolic blood pressure; DBP, diastolic blood pressure; MAP, Mean arterial pressure; HR, heart rate; ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; CI, confidence interval.

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 No. 2023ER368-1) and was registered on the Chinese Clinical Trials. gov (No. ChiCTR2300077778). All participants provided their written informed consent. We confirm our study complies with the Declaration of Helsinki.

Acknowledgments

Yanxia Guo and Zhihua Yao are co-first authors for this study. We would like to thank Dr. Yalan Li for her technical guidance.

Disclosure

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

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