

The Median Effective Dose and Bispectral Index of Remimazolam Tosilate for Anesthesia Induction in Elderly Patients: An Up-and-Down Sequential Allocation Trial

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Purpose: Remimazolam is a new type of ultrashort benzodiazepine drug with an unclear optimal dose for general anesthesia induction in elderly patients aged >60 years. Therefore, this study aimed to determine the effective dose of remimazolam tosylate induction and explore its correlation with the bispectral index (BIS).

Patients and Methods: A total of 42 elderly patients were divided into two age groups: 60–69 (group A) and 70–85 (group B) years. An initial dose of 0.1mg/kg(Group A) and 0.05 mg/kg(Group B) remimazolam tosylate was administered, and the Modified Observer's Assessment of Alertness/Sedation scale was used to assess adequate responses. The dose was calculated using the up-and-down allocation technique based on the previous response. The sequential formula and probit regression model were used to calculate ED50 and BIS50. ED95 was determined using the probit regression model.

Results: The ED50 of remimazolam tosylate for anesthesia induction were 0.088 mg/kg (95% confidence interval [CI] 0.071–0.108) and 0.061 mg/kg (95% CI 0.053–0.069) in groups A and B, respectively. ED95 was 0.118 mg/kg (95% CI 0.103–0.649) and 0.090 mg/kg (95% CI 0.075–0.199) in groups A and B, respectively. The remimazolam tosylate administration could decrease BIS. BIS50 was 86.0 (95% CI 83.7–88.6) and 85.4 (95% CI 84.1–86.8) in groups A and B, respectively.

Conclusion: During the induction process, patients' consciousness should be observed. The dose of remimazolam tosylate could be chosen after careful consideration of individual variations.

Keywords: remimazolam, anesthesia induction, geriatric, up-and-down sequential allocation

Introduction

Remimazolam is a new type of ultrashort benzodiazepine drug that is increasingly applied in clinical anesthesia. Several previous studies reported that benzodiazepines have been confirmed to function as a gamma-aminobutyric acid-A (GABA-A) receptor in the amygdala and reticular activating system binding sites and to change the conformation of chloride channels, resulting in hyperpolarization that inhibits its effects in the central nervous system.^{1,2} Midazolam was the classic benzodiazepine used for sedation and as an anticonvulsant since 1982.³ However, the long-term use of midazolam is associated with disadvantages, namely, drug accumulation and prolonging sedation time.⁴ Remimazolam is a midazolam derivative added with an ester moiety, and besylate and tosylate forms were developed.⁵ It is metabolized by nonspecific tissue esterase enzymes, and the binding ability of its main metabolite CNS7054 to GABA-A receptor decreased significantly.⁵ Studies have shown that its sedative effects can be quickly reversed by flumazenil.⁶ The advantages of remimazolam include a fast onset of action, short recovery time, and stable hemodynamics.¹ Currently, a clinical study of remimazolam mainly focused on the induction and maintenance of non-elderly patients and

endoscopic anesthesia.⁷ The optimal doses required for general anesthesia induction in elderly patients aged >60 years remain unclear. The bispectral index (BIS) is a method used to monitor the hypnotic state, which has been demonstrated to correlate well with sedation levels following induction with propofol. The effect of remimazolam on BIS during induction in elderly patients is not completely understood.

Therefore, this study aimed to determine the effective dose of remimazolam in elderly patients aged 60–85 years using a sequential design and Dixon up-and-down methods and to evaluate the effect of remimazolam on BIS scores.

Materials and Methods

This study was registered in the Chinese Clinical Trial Registry (ChiCTR2100046482). Ethical approval was provided by the Ethics Committee of Capital Medical University, Beijing, China, on April 26, 2021 (No. [2021] 022). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients who participated in this study.

Inclusion and Exclusion Criteria

Due to the physiological deterioration in elderly patients, the efficacy of sedative drugs may be different in various age groups.⁸ Therefore, they were subdivided into two groups according to age: 60–69 (group A) and 70–85 (group B) years. From June to December 2021, 42 elderly patients undergoing elective hepatobiliary surgery were enrolled in this trial. All patients were induced general anesthesia with endotracheal intubation mechanical ventilation. Inclusion criteria were as follows: patients with American Society of Anesthesiologists status of I–III and body mass index (BMI) of 18–30 kg/m². Exclusion criteria were as follows: emergency surgery; hypovolemia; shock; need to be combined with other anesthesia methods; infectious heart disease; need for cardiopulmonary bypass; need for heart, liver, or kidney transplantation; severe liver or kidney impairment; anemia or thrombocytopenia; severe heart disease; poor blood pressure or blood glucose control; difficulty in respiratory tract management; a history of drug abuse and/or alcohol abuse; mental system diseases; or history of allergy to benzodiazepine.

Anesthesia Procedure and Statistical Analysis

Upon entering the operating room, standard vital signs monitoring, including the heart rate, noninvasive blood pressure, peripheral pulse oxygen saturation, anesthesia depth (BIS), and body temperature monitoring were performed. Invasive monitoring can be performed based on the clinical needs. Before the induction of anesthesia, an 18- or 20-G intravenous catheter was placed in the basilic vein, and 3 mL/kg of lactated Ringer's solution was administered as a precharge liquid. Before induction, adequate mask oxygen inhalation was administered. BIS values when awake (BISawake) were recorded after allowing patients to lay down for 5 min. Remimazolam tosylate was administered according to the protocol, and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale was also assessed. After successful sedation, sufentanil of 0.1–0.3 µg/kg and rocuronium of 0.6–1.0 mg/kg were administered consecutively. Endotracheal intubation was performed when analgesia and muscle relaxation were achieved. Propofol was titrated to maintain BIS between 40 and 60, and continuous pump infusion of remifentanyl was maintained at 0.1–0.3 µg/kg/min. In this study, statistical analyses were performed using Microsoft Office Excel 2016 (Microsoft Inc., Washington, USA). ED50 and BIS50 values were determined according to a sequential formula using SPSS software version 25.0 (IBM SPSS Statistics Inc., Chicago, IL) to perform probit regression analysis, paired *t*-test, and Pearson's linear correlations. Figures were prepared using GraphPad Prism version 5.0 (GraphPad Software Inc. San Diego, CA, USA). Statistical significance was set at the *p* value of <0.05.

Identification of ED50 and ED95

The dose distribution was determined using Dixon's modified up-and-down method.^{9–11} The administration regimen was as follows: the initial dose of remimazolam tosylate (Hengrui Pharmaceutical Co., Ltd, Jiangsu China) was set at 0.1 mg/kg in group A, and the dose was designed following the geometric progression with a ratio of 2. The initial dose was injected within 1 min (±5 s) and the MOAA/S score was performed after 1 min. "Successful sedation" is defined as the sedation level maintained at MOAA/S score of 0. Then, the next patient received a low-level dose. Conversely, the MOAA/S score of ≥1 was

defined as “failed sedation,” which the next patient received a high-level dose. In group B, the initial dose of remimazolam tosylate was set at 0.05 mg/kg and designed based on the geometric progression with a ratio of 1.5. Patients with failed sedation at the initial dose would be given half of the initial dose and then scored again. The maximum observation time was 5 min. Until this time, patients who still had failed sedation would take remedial measures by injecting propofol of 0.5–1 mg/kg. The observation was stopped when seven crossover points were observed between successful and failed sedation. Using Dixon’s up-and-down method data, ED50 was determined using two methods, sequential formula, and probit regression model, and only using the probit regression model to determine ED95. These data were expressed as mean and 95% confidence interval (CI).

Determination of BIS50

In this experiment, patients taking remedial measures would be excluded. BIS50 was defined as the BIS associated with 50% of patients who fell asleep. We recorded the lowest BIS in this procedure. The lowest BIS was determined based on an analogy with drug doses and divided into geometric progression for each group. BIS50 could be determined by substituting the geometric progression data into the sequential formula and probit regression model.¹² We still recorded the BIS when the MOAA/S score was 0, which was considered as BIS when the patient is asleep (BISasleep). A paired *t*-test was used to compare changes between BISawake and BISasleep. The relationship between the total dose of remimazolam tosylate, and the decline of BIS was investigated using Pearson’s linear correlations.

Results

The patient characteristic data are listed in Table 1. A total of 43 elderly patients were assessed for study eligibility. One patient in group B was excluded because he refused to participate. Finally, 42 patients were enrolled (Figure 1).

ED50 and ED95

In an effective dose experiment, ED50 of remimazolam tosylate for anesthesia induction was 0.088 mg/kg (95% CI 0.071–0.108) and 0.061 mg/kg (95% CI 0.053–0.069) in groups A and B, respectively, using the sequential method. Then, using the probit regression model, the ED50 of remimazolam tosylate was 0.090 mg/kg (95% CI 0.071–0.107) and 0.063 mg/kg (95% CI 0.049–0.085) in groups A and B, respectively. The ED95 was 0.118 mg/kg (95% CI 0.103–0.649) and 0.090 mg/kg (95% CI 0.075–0.199) in groups A and B, respectively. The Dixon up-and-down plots for each group are shown in Figure 2A and B. The dose-response curve of remimazolam tosylate induction in each group is shown in Figure 3.

BIS50

No patient has taken remedial measures. In the study of the correlation between remimazolam tosylate induction and BIS value, the BIS50 was 86.0 (95% CI 83.7–88.6) and 85.4 (95% CI 84.1–86.8) in groups A and B using the sequential method. Calculated by probit regression, the BIS50 was 88.1 (95% CI 80.4–92.8) and 87.2 (95% CI 80.1–91.5) in groups

Table 1 The Characteristic Data

Variables	Group A (n = 21)	Group B (n = 21)
Age (year)	65.6 ± 2.6	74.38 ± 3.2
Male/female	7/14	9/12
Weight (kg)	64.5 ± 10.4	70.6 ± 7.2
Height (cm)	164.2 ± 7.8	165.1 ± 8.6
BMI (kg/m ²)	23.9 ± 2.2	26.1 ± 2.8
ASA classification [(I/II/III)%]	100/0	85.7/14.3

Note: Data are presented as mean ± standard deviation and number of subjects.

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

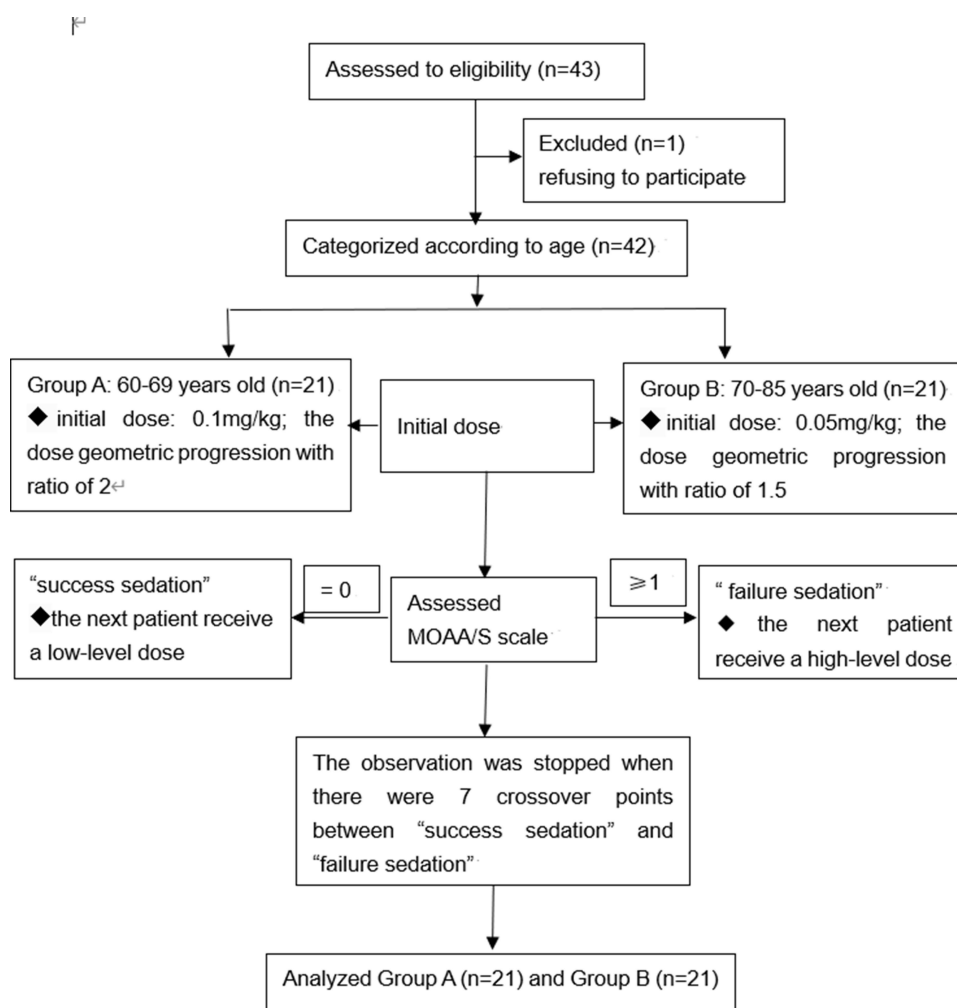


Figure 1 Flow diagram of included participants.

A and B, respectively. According to the paired *t*-test, the BIS value decreased after remimazolam tosilate administration in both groups (mean \pm standard error [19.87 ± 1.56]), $p < 0.001$ in group A and [16.05 ± 1.09], $p < 0.001$ in group B).

The remimazolam tosilate administration could decrease BIS. However, no strong correlations were found between the total dose of remimazolam tosilate and the decline of BIS (Pearson's correlation coefficient, 0.005, $p = 0.055$ in group A; Pearson's correlation coefficient, -0.003 , $p = 0.990$ in group B).

Table 2 summarizes the results of ED50, ED95, and BIS50 in both groups. Appendix 1 shows the specific calculation process used to derive the abovementioned results.

Discussion

Remimazolam is a new ultra-short-acting benzodiazepine intravenous sedation agent.^{1,2} It is a water-soluble and tosilate salt that has been approved for procedural sedation in China.¹³ The experimental drug used in this study was in tosilate form. At present, it is mainly used for endoscopic procedure sedation, such as colonoscopy and upper gastrointestinal endoscopy.⁷ Only a few reports applied remimazolam for general anesthesia, and the inclusion population of these reports focused on non-elderly patients.^{14,15} Therefore, clinical medication experience and recommended effective dose are lacking for elderly patients. As already known, elderly patients with reduced reserves of various physiological functions have poor anesthesia tolerance, and the risk of anesthesia increases to a certain extent.¹⁶ Thus, anesthesia should be more individualized and cautiously administered. In this study, the ED50 and ED95 of remimazolam tosilate for general anesthesia induction were explored in elderly patients aged >60 years for the first time and set the initial dose to 0.1 mg/kg or 0.05 mg/kg. Furthermore, to obtain a more accurate and effective

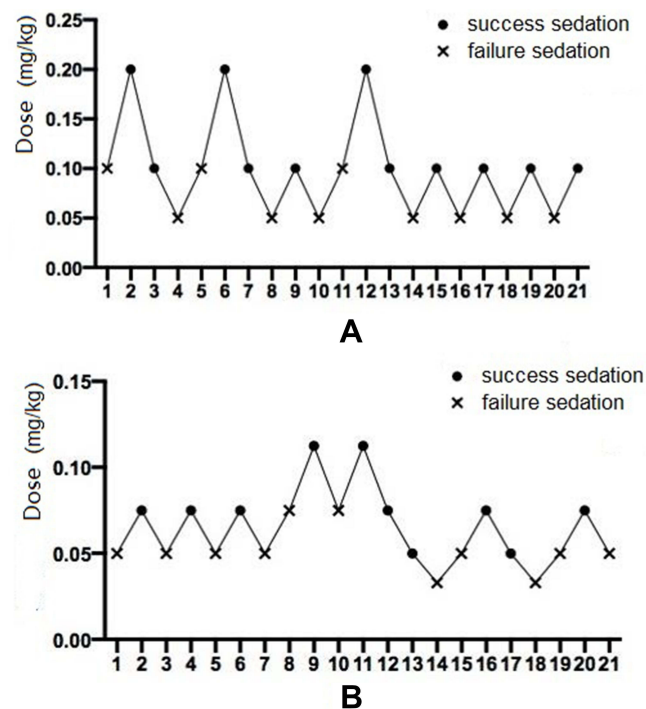


Figure 2 The Dixon up-and-down plots demonstrating dose reported as successful sedation (point) and failed sedation (fork) in groups A (**A**) and B (**B**).

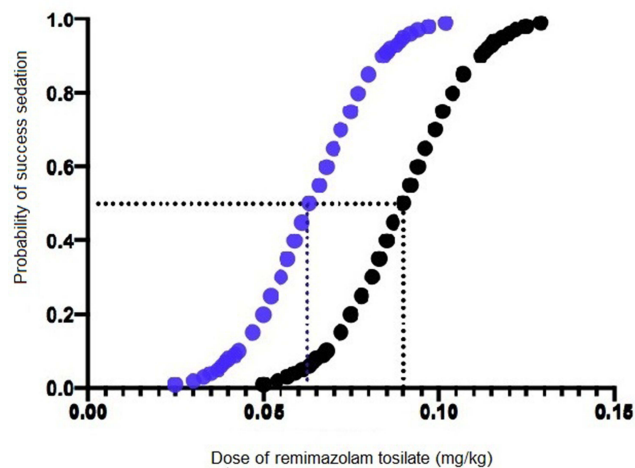


Figure 3 The dose-response curve of remimazolam tosylate induction in each group. Black point curve represents Group A and blue point curve represents Group B.

induction dose, elderly patients were also grouped according to age, and ED50, ED95, and BIS50 were determined for patients aged 60–69 and 70–85 years, respectively. Liu administered an initial dose of 0.15 mg/kg of remimazolam tosylate for sedation in elderly patients undergoing colonoscopy and obtained a procedural success rate of 96.52%.¹⁷ This is consistent with our ED95 and its CIs. Moreover, results calculated using two statistical methods are similar. Therefore, our data are relatively reliable and are hoped to provide effective information for the use of remimazolam tosylate in inducing general anesthesia in elderly patients. The results may pave the way for more clinical research and follow-up studies in the future. The safety and efficacy of remimazolam tosylate will be the focus of our follow-up studies.

In this study, BIS values of remimazolam tosylate were also analyzed. BIS monitoring is widely used clinically as a monitoring indicator to quantify the extent of sedation.¹⁸ Previous studies have shown that propofol is rapidly metabolized in patients and that changes in its plasma concentration or effector compartment concentration are strongly

Table 2 Summary List of Results Between the Two Groups

		Group A	Group B
ED50	Sequential method	0.088 (0.071–0.108)	0.061 (0.053–0.069)
	Probit regression analysis	0.090 (0.071–0.107)	0.062 (0.049–0.085)
ED95	Probit regression analysis	0.118 (0.103–0.649)	0.090 (0.075–0.199)
BIS50	Sequential method	86.0 (83.7–88.6)	85.4 (84.1–86.8)
	Probit regression analysis	88.1 (80.4–92.8)	87.2 (80.1–91.5)

Note: The ED50, ED95, and BIS50 with their 95% confidence interval.

correlated with sedation changes noted through BIS monitoring.^{19–21} A prospective trial focusing on the propofol concentration in Chinese patients showed that BIS associated with a 50% probability of loss of consciousness was 58 (58–59).²² In our study, although remimazolam tosylate injection for induction could reduce BIS, BIS50 was higher using remimazolam tosylate than that using propofol. Therefore, BIS cannot be used as an index to judge whether patients fall asleep during the remimazolam tosylate administration to induce general anesthesia.

The present study has certain limitations. For instance, only a few studies have reported the efficacy and safety of remimazolam tosylate to induce general anesthesia in elderly patients. Further studies should aim to elucidate the appropriate dose in different populations. Therefore, our study should be considered exploratory. Furthermore, individual differences in elderly patients might cause variations in drug metabolism. Finally, the study was limited to the relatively healthy elderly patients undergoing elective surgeries. Further research must focus on highly at risk elderly people.

Conclusion

In conclusion, the ED50 of remimazolam tosylate for anesthesia induction was 0.088 mg/kg (95% CI 0.071–0.108) and 0.061 mg/kg (95% CI 0.053–0.069) in elderly patients aged 60–69 and 70–75 years, respectively. The ED95 was 0.118 mg/kg (95% CI 0.103–0.649) and 0.090 mg/kg (95% CI 0.075–0.199) in elderly patients aged 60–69 and 70–85 years, respectively. Only a slight correlation was observed between the decline of BIS value and falling asleep when inducing general anesthesia using remimazolam tosylate. BIS value cannot be used as an indicator of patients falling asleep. During the induction process, patients' consciousness should be observed. The remimazolam tosylate dose could be selected after carefully considering individual variations.

Data Sharing Statement

Data related to this study can be obtained by contacting the corresponding author if reasonable.

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Disclosure

The authors declare no conflict interests. The Hengrui Pharmaceutical Co., Ltd had no role in the conduct and analysis of the trial. This manuscript was supported by grants from Beijing Municipal Health Commission (code: Jing2019-2).

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