Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Dose-Response Study of Remimazolam Combined With Remifentanil for Attenuating Stress Response During Laryngeal Mask Airway Insertion in Elderly Female Patients: A Prospective Double-Blinded Study

Qiang Xu*, Jing Qian*, Su-Qin Zhang, Feng Xia, Hui-Jing Hu, Fei Xiao

Department of Anesthesia, Jiaxing University Affiliated Women and Children Hospital, Jiaxing City, Zhejiang Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hui-Jing Hu; Fei Xiao, Department of Anesthesia, Jiaxing University Affiliated Women and Children Hospital, East Zhonghuang Road, Jiaxing City, People's Republic of China, Tel +86 573 83963131-8300, Email hhj08mz@163.com; 13706597501@163.com

Background: Optimum dose of remimazolam for inducing loss of consciousness in elderly patients has been suggested by prior studies. Opioids can enhance their sedative effects, thereby permitting dose reduction. However, the dose-response of remimazolam when combined remifentanil for attenuating stress response during laryngeal mask airway (LMA) insertion in elderly female patients is still unknown. Moreover, the ideal dose of medications is especially critical in elderly patients due to their compromised cardiopulmonary function. The objective of this study was to determine the median effective dose (ED50) and ED95 of remimazolam in inhibiting the stress response associated with LMA insertion.

Methods: Sixty aged ≥ 65 and < 80 years old female patients were randomized allocated into 1 of 4 groups receiving doses of 0.2, 0.25, 0.3, and 0.35 mg/kg remimazolam. Following a dosage of 2.0 ng/mL of remifentanil, patients received different doses of remimazolam. Effective dose is defined as the prevention of stress response associated with LMA insertion, characterized by a post-sedation induction SBP variation < 20% of baseline value, jaw relaxation and absence of patient body motion during the initial 2 minutes following LMA insertion. Probit regression analysis was utilized to estimate the ED50 and ED90 values.

Results: The ED50 and ED95 of effective remimazolam of general induction for elderly female patients not suffer intubation stress response were 0.24 mg/kg (95% CI 0.20–0.27 mg/kg) and 0.37 mg/kg (95% CI 0.32–0.49 mg/kg), respectively. The incidence of hypotension was 33.3% (5/15), 46.7% (7/15), 73.3% (11/15), and 80% (12/15) in the four groups, respectively.

Conclusion: The ED50 and ED95 values of intravenous remimazolam for preventing stress response during LMA insertion were 0.24 and 0.37 mg/kg, respectively in elderly female.

Trial Number and Registry Url: Registration number, ChiCTR2400083990, https://www.chictr.org.cn/showproj.html?proj=229006.

Keywords: remimazolam, remifentanil, dose-response, stress response, elderly patients

Introduction

Remimazolam, an ultrashort-acting benzodiazepine, exhibiting gentle respiratory depression, stable hemodynamics, quick initiation and rapid metabolism, due to its non-accumulative properties in the body and independence from hepatic or renal function for metabolism, is growing popular in general anesthesia.[1] Previous studies have emphasized the advantageous hemodynamic properties of this substance in comparison to propofol, particularly among patients classified

Received: 3 September 2024
Accepted: 11 February 2025
Published: 5 March 2025

as ASA class I or II.[2,3] Despite the established safety profile of remimazolam in elderly patients, there remains a need for further investigation into its optimal dosage for clinical application, particularly in this specific population.[4–6]

Several studies have observed varying doses required for inducing sedation during the induction process and proposed the optimal (0.19–0.25, and 0.14–0.19 mg kg^{-1} in patients aged 60–80, and >80 years) or 95% effective dose (ED95, 0.118 mg/kg for patients aged 60–69 years and 0.090 mg/kg for patients aged 70–85 years.) of remimazolam specifically for elderly patients without administering any other drugs.[7,8] However, Arime et al[9] found that remimazolam frequently proves inadequate in suppressing the response to jaw thrusting, rendering it unsuitable as an induction agent for routine supraglottic airway insertion without concurrent administration of either a neuromuscular blocking agent or an opioid. To the best of our knowledge, no previous studies have investigated the dose-response relationship of remimazolam in mitigating the stress response associated with LMA insertion when administered alongside a target-controlled intravenous infusion of remifentanil at 2 ng/mL (as established in prior research).[10] Therefore, the objective of this study was to determine the median effective dose (ED50) and ED95 of remimazolam, when combined with 2 ng/mL remifentanil, in inhibiting the stress response associated with LMA insertion in elderly female patients. Our hypothesis is that the optimal dose for this procedure may be higher than previous studies reported for inducing sedation during the induction process in elderly patients, as the stimulation was greater with laryngeal mask insertion.

Methods

The current study was approved by the Ethics Committee of Jiaxing University Affiliated Women and Children Hospital (IRB: 2024-Y-32). Prior to patient enrollment, we prospectively registered this study in the Chinese Clinical Trial Registry (https://www.chictr.org.cn/showproj.html?proj=229006, registration number, ChiCTR2400083990) on May 8th 2024. And Written Informed Consent was obtained from all participants enrolled in this study. This study was performed according to the principles of the Declaration of Helsinki.

We enrolled 70 female parturients aged ≥ 65 and < 80 years old, with a BMI ranging from 18 to 35 and classified as American Society of Anesthesiologists physical status II–III, who were scheduled for hysteroscopic surgery. Patients with comorbidities such as myasthenia gravis, schizophrenia, severe depression, uncontrolled hypertension (systolic blood pressure, SBP ≥160mmHg), and diabetes (blood glucose ≥11.1mmol/L) were excluded from the study. Additionally, individuals with chronic pain requiring long-term use of analgesics or psychiatric medications, those exhibiting alcohol abuse, and those experiencing an allergic reaction to remimazolam were also excluded.

Patients were randomly assigned to one of four groups, receiving doses of 0.2, 0.25, 0.3, and 0.35 mg/kg remimazolam; it was determined based on a comprehensive review of relevant literature[7,8] and our extensive clinical expertise (The dose was adjusted following our preliminary experiment; the initially registered doses ranged from 0.25 to 0.40 mg/kg). The randomized number sheet was generated using Microsoft Excel (Redmond, Washington), and subsequently concealed within opaque envelopes prior to being opened following the enrollment of each parturient. The study drug was prepared by a designated anesthesiologist assistant who possesses knowledge of patient grouping and is not involved in patient management or data collection. To ensure blinding of investigators, remimazolam was accurately diluted into an identical 20 mL syringe.

Patients received no premedication. Upon the patient's arrival at the operating theater, a comprehensive standard vital sign monitoring protocol was implemented, encompassing noninvasive blood pressure measurement (Baseline SBP and heart rate (HR) was determined by calculating the mean value of three consecutive measurements taken at 3-minute intervals), peripheral pulse oxygen saturation assessment, electrocardiography, and Bispectral Index (BIS). Then a peripheral intravenous access was established using an 18-gauge intravenous catheter, the preoperative hydration was achieved by administering 3 mL/kg of lactated Ringer's solution, warmed to 37°C, prior to anesthesia induction.

According to the protocol, patients in each group will receive a dosage of 2.0 ng/mL of remifentanil and then 1 minutes later varying doses of remimazolam (Hengrui Pharmaceutical Co., Ltd, Jiangsu China) at 0.2, 0.25, 0.3, and 0.35mg/kg prepared in an identical 20 mL syringe administered in 1 minute. During the initial 5 minutes following anesthesia induction, the Modified Observer's Assessment of Alertness/Sedation[11] (MOAA/S, 5 = responds readily to name spoken in normal tone; 4 = a sluggish reaction to name spoken in normal tone; 3 = responds only name is called loudly and/or repeatedly; 2 = responds only after mild prodding or shaking; 1 = responds only after painful trapezius

squeeze; 0 = does not respond to painful trapezius squeeze) was evaluated at 1-min intervals, with the BIS value serving as a supplementary measure to determine sedation depth. If a MOAA/S score of 0 is obtained within 5 minutes following intravenous administration of remimazolam, a size of 3.0–4.0 LMA was inserted to facilitate mechanical ventilation. Conversely, in cases where the MOAA/S score was > 0, an additional dose of remimazolam 0.1 mg/kg was administered, repeated if necessarily; however, these instances were considered as failures to successfully insert LMA due to inadequate sedation induction.

The primary outcome was the effective or ineffective dosage required to inhibit the stress response associated with LMA insertion. An effective dose is defined as the prevention of stress response associated with LMA insertion. Stress response was defined as the symptom characterized by a post-sedation induction SBP variation > 20% of baseline value, jaw not relaxation and presence of body motion during the initial 2 minutes following LMA insertion. Otherwise, it was regarded as an ineffective dose. In the event of an unsuccessful case, a supplementary dose of remimazolam was administered at the discretion of the attending anesthesiologist. Secondary outcome included SBP, heart HR, side effects, including hypertension (values >120% baseline value), hypotension (values <80% baseline value), bradycardia (HR< 50bpm) and tachycardia (HR> 100bpm), and induction time (period from intravenous injection to LMA insertion) and recovery time (period from injection cease to extubation).

Sample Size Calculation

The sample size was determined based on our preliminary experiment, for the 4 groups with different dose of 0.2, 0.25, 0.3, 0.35 mg/kg remimazolam, the proportions of effective prevention of stress response associated with LMA insertion were 20%, 60%, 73%, and 87%, respectively. Consequently, we determined that a total of 32 patients (8 patients per group) would be necessary to achieve a statistical power of 90% in detecting a linear trend in the proportion of patients exhibiting effective prevention of stress response associated with LMA insertion across the groups. This analysis was performed using a Z test with continuity correction and a significance level set at 0.05. To account for potential dropouts, the sample size was subsequently increased to include 15 patients in each group.

Statistical Analysis

The distribution of continuous data was assessed using the Kolmogorov–Smirnov test.

The demographic data of patients, which followed a normal distribution, were expressed as means ± standard deviation (SD) and assessed for statistical significance using one-way analysis of variance (ANOVA), followed by pairwise comparisons using the Post hoc Bonferroni test. The data, which did not follow a normal distribution, were reported as the median and interquartile range (IQR). Statistical analysis involved the utilization of the Kruskal–Wallis test, with post hoc.

Dunn's tests for pairwise group comparisons. Categorical variables were presented as absolute numbers and percentages. The incidence of hypotension and reactive hypertension was assessed using the Cochran-Armitage $\chi 2$ trend test, in accordance with established statistical methods. In cases where a statistically significant overall difference among groups was observed, pairwise comparisons were subsequently conducted using $\chi 2$ tests.

The analysis of SBP changes within the initial 10 minutes after LMA insertion was conducted utilizing a technique based on summary measures.[12,13] The integral of values plotted against time for each group was determined using the trapezoidal rule, and subsequently compared between groups using one-way analysis of variance.[12,13] The dose groups were naturally ordered; thus, a linear trend analysis was employed to examine the presence of a linear trend across these groups.

The probit regression analysis was utilized to estimate the ED50 and ED90 values, which represent the doses necessary for effectively preventing stress response during LMA insertion in 50% and 90% of patients, respectively. The Pearson $\chi 2$ test for goodness-of-fit was utilized to evaluate the adequacy of the probit model in fitting the data. The statistical significance was determined for P values less than 0.05 (two-tailed). Adjusted P values were reported when Bonferroni corrections were applied. The statistical analyses were conducted using IBM SPSS Statistics for Windows version 22.0 (IBM Corp), GraphPad Prism version 5.0 (GraphPad Software Inc), and Microsoft Excel (Microsoft Corporation).

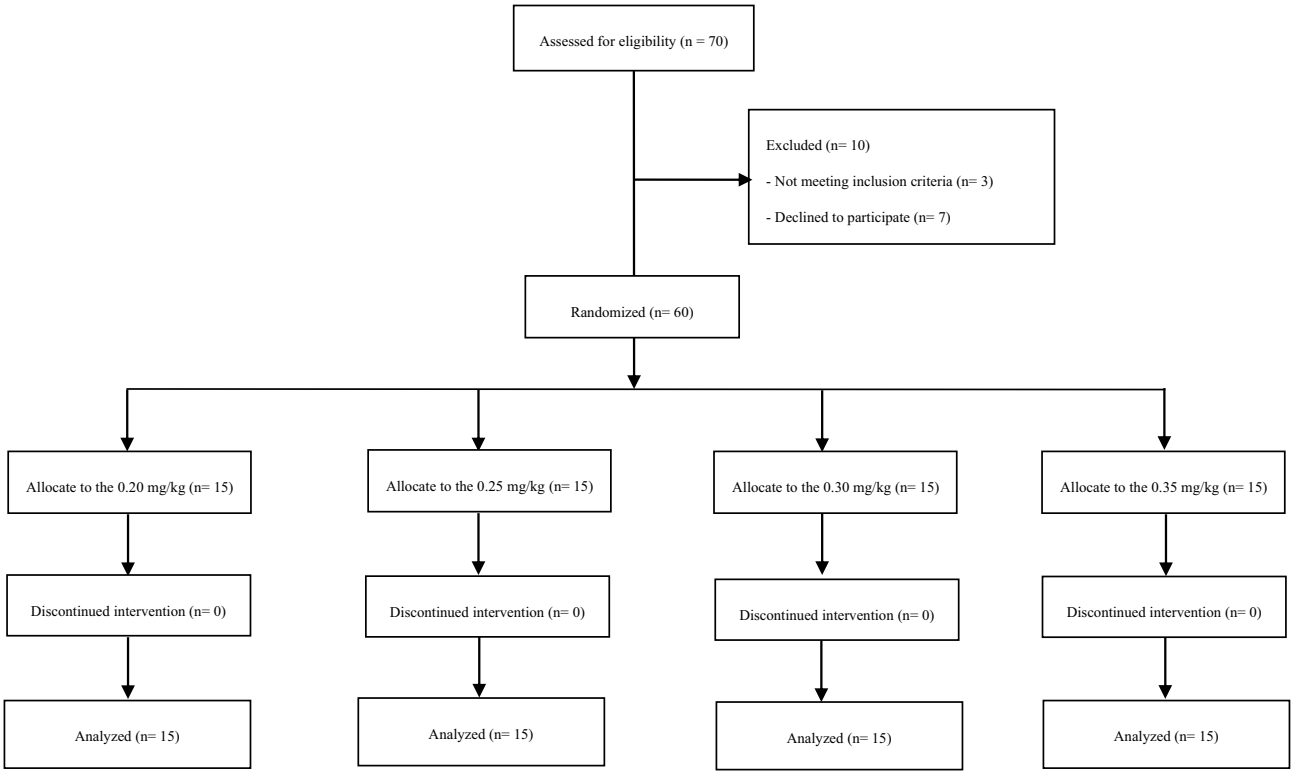

Figure 1 CONSORT flow diagram.

Results

A total of 70 patients were enrolled to assess eligibility, with 7 declining participation and 3 not meeting the inclusion criteria. Finally, a total of 60 patients were randomly assigned to four groups and included in the final intention-to-treat analysis. The CONSORT diagram illustrating the patient allocation is presented in Figure 1. The demographic characteristics of the patients were presented in Table 1, and no statistically significant differences were observed among the groups.

In group 0.20, 26.7% (4/15) of patients received effective laryngeal mask airway insertion and not experienced an intubation stress response, followed by 60% (9/15) in group 0.25, 73.3% (11/15) in group 0.30, and finally 93.3% (14/15) in group 0.35. A significant linear trend was observed between the dose of remimazolam and successful insertion of the laryngeal mask airway across all groups, $P < 0.0001$. The MOAA/S score, induction and recovery time, and stress response of laryngeal mask airway insertion in patients was summarized in Table 2. The ED50 and ED95 of effective remimazolam for patients not suffer intubation stress response were 0.24 mg/kg (95% CI 0.20–0.27 mg/kg) and 0.37 mg/kg (95% CI 0.32–0.49 mg/kg), respectively. The dose-

Table 1 Patient Characteristics

Assigned Dose (mg/kg)	0.20 (n = 15)	0.25 (n = 15)	0.30 (n = 15)	0.35 (n = 15)
Age (years)	67.07±4.06	64.73±4.50	66.80±5.20	66.07±3.79
Height (cm)	157.93±4.98	158.07±5.54	158.00±3.16	157.53±5.59
Weight (kg)	60.85±7.12	59.05±9.92	60.35±8.29	56.59±6.58
BMI (kg/m^2)	24.34±2.03	25.53±3.06	24.14±2.91	22.77±1.99
SBP (mmHg)	133.80±15.32	125.73±9.87	129.13±13.01	128.80±13.63
HR (bpm)	76.60±5.79	81.80±8.64	81.33±7.03	76.07±9.84
Operation duration (min)	29.33±11.30	32.07±7.79	32.33±13.18	30.33±9.02

Note: Values are mean ± SD or number of patients, n (%).
Abbreviation: BMI, body mass index.

Table 2 MOAA/S Score, Stress Response, Induction and Recovery Time

	0.20 (n = 15)	0.25 (n = 15)	0.30 (n = 15)	0.35 (n = 15)	*P* value
MOAA/S > 0	2 (13.3%)	1 (6.7%)	0 (0%)	0 (0%)	0.063
Jaw not relaxation	9 (60.0%)[a]	4 (26.7%)	4 (26.7%)	1 (6.7%)	0.002
Body motion	2 (13.3%)	1 (6.7%)	0 (0%)	0 (0%)	0.063
Hypertension	2 (13.3%)	1 (6.7%)	0 (0%)	0 (0%)	0.063
Induction time, min	2 (2–3)	2 (2–3)	2 (2–2)	2 (2–2)	0.132
Recovery time, min	6.1 (2.4)	7.0 (2.6)	7.5 (2.2)	8.5 (1.9)[b]	0.045

Notes: Values are presented as mean (standard deviation), Median (interquartile range) number of patients, n (%). Categorical data were analyzed using the Cochran–Armitage $\chi 2$ test for trend. Hypertension was defined as systolic blood pressure >120% of baseline value. [a]Compared with group 0.35, p = 0.005; [b]Compared with groups 0.20, adjusted p = 0.034.

response curve of remimazolam, obtained through probit analysis, is presented in Figure 2. The Pearson goodness-of-fit $\chi 2$ test yielded a satisfactory fit for the probit model ($P = 0.803$).

The fluctuations in SBP over the period during the first 10 minutes are depicted in Figure 3, representing the four distinct groups. The analysis revealed a significant difference in systolic blood pressure (SBP) over time among the groups ($P < 0.001$), and a notable linear trend was also observed across the dose groups ($P < 0.001$). The incidence of hypotension was 33.3% (5/15), 46.7% (7/15), 73.3% (11/15), and 80% (12/15) in the four groups, respectively. There was a significant trend in the incidence of hypotension across groups, $P = 0.025$. No patients in groups 0.20 and 0.25 required ephedrine for the treatment of hypotension, whereas three patients in group 0.30 and five patients in group 0.35 necessitated ephedrine administration. Other side effects, including hypertension, bradycardia and tachycardia were summarized in Table 3, and no significant difference were observed among groups.

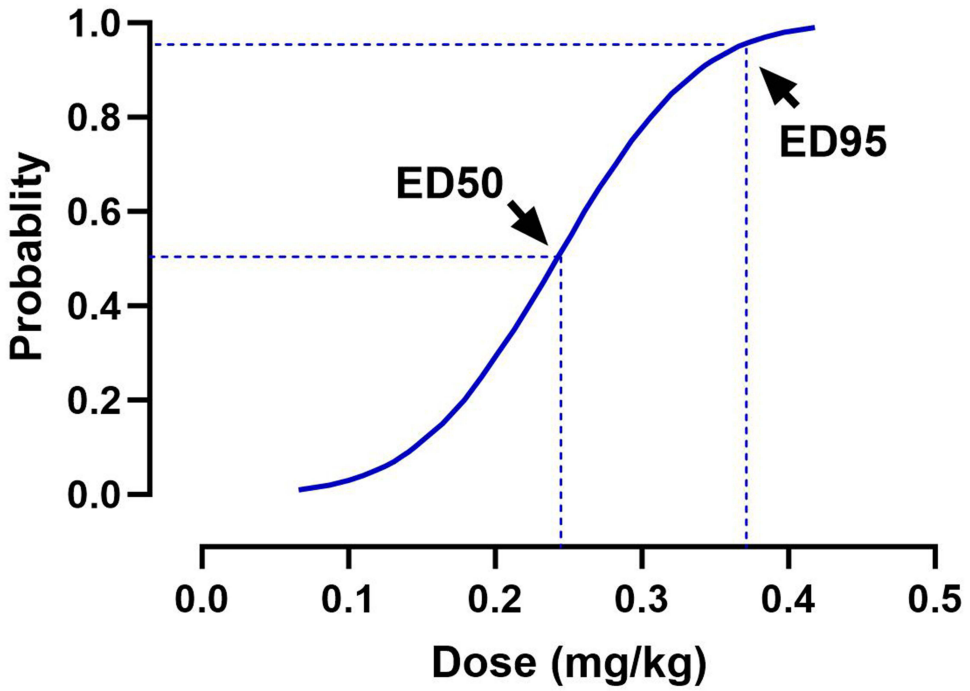

Figure 2 Dose-response curve of remimazolam, obtained through probit analysis. The ED50 and ED95 of effective remimazolam of general induction for patients not suffer intubation stress response were 0.24 mg/kg (95% CI 0.20–0.27 mg/kg) and 0.37 mg/kg (95% CI 0.32–0.49 mg/kg), respectively.

https://doi.org/10.2147/DDDT.S494426

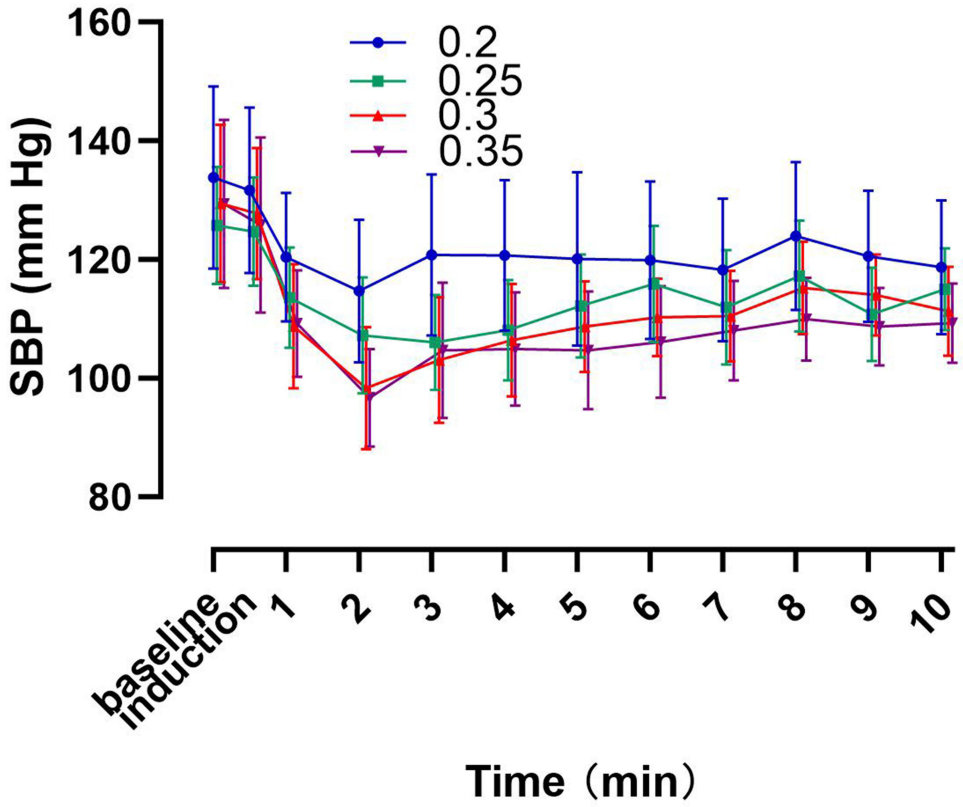

Figure 3 Fluctuations in SBP over the period during the first 10 minutes. The observed differences in the area under the curve (mean ± SD) were found to exhibit statistically significant variations across the different groups (1208 ± 28, 1126 ± 19, 1100 ± 19 and 1076 ± 20 min·mm Hg in group 0.2, 0.25, 0.3 and 0.35, respectively, $P < 0.0001$), and a significant liner trend was observed among groups, $P < 0.0001$.

Discussion

In this study, we compared four different doses of remimazolam combined with 2.0 ng/mL remifentanil for the induction of sedation and prevention of stress response associated with LMA insertion in elderly female patients. Our findings revealed that the median effective dose (ED50) and 95% effective dose (ED95) values of intravenous remimazolam for preventing stress response during LMA insertion were 0.24 mg/kg (95% CI 0.20–0.27 mg/kg) and 0.37 mg/kg (95% CI 0.32–0.49 mg/kg), respectively, which are notably higher than previously reported doses used for inducing sedation.[7,8] In addition, our data revealed a notable blood pressure fluctuation and an increased occurrence of hypotension in patients administered with a high dosage of remimazolam.

In a recent study, the investigation of remimazolam for anesthesia induction in elderly patients revealed ED95 values of 0.118 mg/kg (95% CI, 0.103–0.649) and 0.090 mg/kg (95% CI, 0.075–0.199) for patients aged 60–69 years and 70–85 years, respectively, based on MOAA/S score assessments.[7] Chae et al conducted a randomized, prospective, double-blind

Table 3 Side Effects

	0.20 (n = 15)	0.25 (n = 15)	0.30 (n = 15)	0.35 (n = 15)	*P* value
Hypertension	2 (13.3%)	1 (6.7)	0 (0)	0 (0)	0.063
Hypotension	5 (33.3%)	7 (46.6%)	11 (73.3%)	12 (80.0%)[a]	0.003
Tachycardia	4 (26.7%)	3 (20%)	3 (20%)	1 (6.7%)	0.179
Bradycardia	2 (13.3%)	0 (0%)	1 (6.7%)	2 (13.3%)	0.835

Notes: Values are presented as number of patients, n (%). Categorical data were analyzed using the Cochran–Armitage $\chi 2$ test for trend. Reactive hypertension was defined as systolic blood pressure >120% of baseline value.
[a] $P = 0.025$.

study and proposed that the optimal doses of remimazolam without any analgesics for inducing loss of consciousness were 0.25–0.33 mg/kg, 0.19–0.25 mg/kg, and 0.14–0.19 mg/kg for patients aged <40 years, 60–80 years, and >80 years, respectively.[8] To enhance the understanding of remimazolam's application in LMA insertion among elderly female patients, we conducted a comprehensive dose-randomized allocation study to provide detailed information (from ED1 to ED99) on remimazolam administration during LMA insertion. The determined ED95 in this study was found to be 0.37 mg/kg, which notably exceeds the induction threshold reported in previous studies solely resulting in loss of consciousness. Due to interindividual variability in pharmacology response, we have also included the ED50 value, which represents the minimum effective dose for guiding clinical reference. The varying incidence of hypotension and fluctuations in systolic blood pressure observed within the first 10 minutes among different groups emphasize the significance of tailoring patient care on an individual basis.

Due to the ideal dose of medications is especially critical in elderly patients due to their compromised cardiopulmonary function. Therefore, this study provides a comprehensive dose-response curve (Figure 2) for clinical reference, aiming to support the determination of the optimal dose for elderly female patients undergoing LMA insertion. Studies have demonstrated that the sole administration of remimazolam is not an appropriate agent for inducing anesthesia during uncomplicated supraglottic airway device placement.[9] This study proposes a novel strategy for the administration of clinical anesthesia in elderly patients.

In addition to demonstrating a comprehensive dose-response relationship of remimazolam in preventing stress response during LMA insertion, our findings indicate that the incidence of remimazolam-induced hypotension is dose-dependent. The findings from our study indicate that careful monitoring of hemodynamic changes is necessary when administering high doses of remimazolam to elderly patients, despite its demonstrated lower hemodynamic effects compared to propofol.[14–17]

When combined with 4 μg/kg fentanyl and 0.15 mg cisatracurium, using a biased coin design method, Qu et al[18] determined that the effective dose (ED95) of remimazolam for inhibiting endotracheal intubation response in frail and non-frail elderly patients was found to be 0.297 mg/kg and 0.331 mg/kg, respectively, which aligns with the findings of this current study. Guo et al[19] conducted a clinical trial using the up-and-down sequential method, incorporating varying doses of fentanyl. The study compared ED50 values and demonstrated that concurrent administration of fentanyl dose-dependently reduces the required dosage of remimazolam for sedative gastroscopy in elderly patients. However, the up-and-down method, while effective in determining efficiency ratios, is not suitable for guiding dosage decisions. The present study, using dose randomized allocation method, not only provides the ED95 as a guiding dose, but also offers a comprehensive dose-response curve, thereby furnishing additional clinical reference information compared to their previous research.

Importantly, previous studies investigating the dosages of remimazolam for sedation induction in elderly patients failed to consider the concurrent administration of any sedative adjuvants, such as opioids and dexmedetomidine.[7,8,20] Our study presents innovative evidence of the dose-response relationship of remimazolam for inhibiting the stress response during LMA insertion when combined with remifentanil. This finding addresses a critical research gap in clinical practice. However, it is important to acknowledge that different institutions may employ varying doses and adjuvants, thereby resulting in the variability of the optimal remimazolam dose across diverse clinical scenarios. Therefore, further investigations are warranted to enhance the clinical utility of remimazolam.

We acknowledge that there are some limitations in the current study. First, the study did not include patients aged over 80 years, and further research should focus on the super-elderly population. Second, it is important to note that this study was conducted at a single medical facility with a limited sample size and aimed to determine the ED50 and ED95 of remimazolam specifically in elderly individuals undergoing LMA insertion. Therefore, its applicability is constrained, and additional research is necessary to establish the optimal dosage for different clinical conditions. Finally, the older adults included in our study exhibited a relatively favorable state of health, thus necessitating future investigations into the coexistence of medical conditions among elderly patients, as certain medical comorbidities are inevitable with advancing age.

Conclusion

In conclusion, the ED50 and ED95 values of intravenous remimazolam for preventing stress response during LMA insertion were 0.24 and 0.37 mg/kg in elderly female patients underwent hysteroscopic surgery. The incidence of hypotension induced by remimazolam is dose-dependent that necessitates vigilant monitoring of hemodynamic changes by clinical anesthesia providers, particularly in elderly patients when administering high doses, to avoid this adverse effect.

Abbreviations

ASA, American Standards Association; BMI, Body mass index; BIS, Bispectral index; ED50, Median effective dose; ED95, 95% effective dose; MOAA/S, Modified Observer's Assessment of Alertness/Sedation.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding authors on reasonable requests.

Acknowledgments

The authors thank all the staff at the Department of Operating Room of Jiaxing University Affiliated Women and Children Hospital, Jiaxing, China, for their help in this study.

Author Contributions

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

Funding

This work was supported by Scientific Technology Plan of Zhejiang Provincial Health Commission (2022KY1264).

Disclosure

The authors declare that they have no competing interests.

References

1. Lu Z, Zhou N, Li Y, Yang L, Hao W. Up-down determination of the 90% effective dose (ED90) of remimazolam besylate for anesthesia induction. *Ann Palliat Med*. 2022;11(2):568–573. doi:10.21037/apm-22-89
2. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anaesth*. 2020;34(4):543–553. doi:10.1007/s00540-020-02788-6
3. Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): results of a multicenter, randomized, double-blind, parallel-group comparative trial. *J Anesth*. 2020;34(4):491–501. doi:10.1007/s00540-020-02776-w
4. Liu X, Ding B, Shi F, et al. The Efficacy and safety of remimazolam tosilate versus etomidate-propofol in elderly outpatients undergoing colonoscopy: a prospective, randomized, single-blind, non-inferiority trial. *Drug Des Devel Ther*. 2021;15:4675–4685. doi:10.2147/DDDT.S339535
5. Nakanishi T, Sento Y, Kamimura Y, Tsuji T, Kako E, Sobue K. Remimazolam for induction of anesthesia in elderly patients with severe aortic stenosis: a prospective, observational pilot study. *BMC Anesthesiol*. 2021;21(1):306. doi:10.1186/s12871-021-01530-3
6. Chen X, Sang N, Song K, et al. Psychomotor recovery following remimazolam-induced sedation and the effectiveness of flumazenil as an antidote. *Clin Ther*. 2020;42(4):614–624. doi:10.1016/j.clinthera.2020.02.006
7. Liu M, Sun Y, Zhou L, Feng K, Wang T, Feng X. The median effective dose and bispectral index of remimazolam tosilate for anesthesia induction in elderly patients: an up-and-down sequential allocation trial. *Clin Intervent Aging*. 2022;17:837–843. doi:10.2147/CIA.S364222
8. 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
9. Arime H, Asai T, Saito T, Okuda Y. Remimazolam: a randomized controlled study of its suitability for insertion of a supraglottic airway. *J Anesth*. 2023;37(5):762–768. doi:10.1007/s00540-023-03231-2

10. Goo EK, Oh AY, Cho SJ, Seo KS, Jeon YT. Optimal remifentanil dosage for intubation without muscle relaxants in elderly patients. *Drugs Aging*. 2012;29(11):905–909. doi:10.1007/s40266-012-0019-y
11. Antonik LJ, Goldwater DR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled Phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): part I. Safety, efficacy, and basic pharmacokinetics. *Anesthesia Analg*. 2012;115(2):274–283. doi:10.1213/ANE.0b013e31823f0c28
12. Senn S. Analysis of serial measurements in medical research. *BMJ*. 1990;300(6725):680. doi:10.1136/bmj.300.6725.680
13. Xiao F, Shen B, Xu WP, Feng Y, Ngan Kee WD, Chen XZ. Dose-response study of 4 weight-based phenylephrine infusion regimens for preventing hypotension during cesarean delivery under combined spinal-epidural anesthesia. *Anesthesia Analg*. 2020;130(1):187–193. doi:10.1213/ANE.0000000000004092
14. Chen D, Liao M, Wu XR, Zhao TY, Sun H. Comparison of efficacy and safety of equivalent doses of remimazolam versus propofol for gastroscopy anesthesia in elderly patients. *Sci Rep*. 2024;14(1):7645. doi:10.1038/s41598-024-58294-2
15. Ye E, Wu K, Ye H, et al. Comparison of 95% effective dose of remimazolam besylate and propofol for gastroscopy sedation on older patients: a single-centre randomized controlled trial. *Br J Clin Pharmacol*. 2023;89(11):3401–3410. doi:10.1111/bcp.15839
16. Ahmer W, Imtiaz S, Alam DM, et al. Remimazolam versus propofol for sedation in gastrointestinal endoscopy and colonoscopy within elderly patients: a meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol*. 2024;80(4):493–503. doi:10.1007/s00228-024-03624-6
17. Barbosa EC, Espírito Santo PA, Baraldo S, Meine GC. Remimazolam versus propofol for sedation in gastrointestinal endoscopic procedures: a systematic review and meta-analysis. *Br J Anaesth*. 2024;132(6):1219–1229. doi:10.1016/j.bja.2024.02.005
18. Qu L, Liu M, Ouyang R, et al. Determination of the 95% effective dose of remimazolam tosylate in anesthesia induction inhibits endotracheal intubation response in senile patients. *Front Pharmacol*. 2023;14:1136003. doi:10.3389/fphar.2023.1136003
19. Guo Y, Yao Z, Feng Y, Wang D, Wang Y, Lin J. ED50 and ED95 of remimazolam tosilate combined with different doses of fentanyl in elderly patients for painless gastroscopy. *Drug Des Devel Ther*. 2024;18:2347–2356. doi:10.2147/DDDT.S462607
20. Oh J, Park SY, Lee SY, et al. Determination of the 95% effective dose of remimazolam to achieve loss of consciousness during anesthesia induction in different age groups. *Korean J Anesthesiol*. 2022;75(6):510–517. doi:10.4097/kja.22331