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CLINICAL TRIAL REPORT

The Impact of Fentanyl on the Effective Dose of Remimazolam-Induced Sedation in Elderly Female Patients: An Up-and-Down Sequential Allocation Trial

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Purpose: This study aimed to investigate the influence of fentanyl on the effective dose of remimazolam-induced sedation in elderly female patients undergoing general anesthesia.

Patients and Methods: Sixty female patients aged 65–80 years undergoing selective general anesthesia were randomized into two groups: Group R+F received an initial dose of remimazolam (7.5 mg) with fentanyl (1 μg/kg), while Group R received remimazolam alone. Dosing adjustments (±2.5 mg) were made based on the response of the preceding patient using the up-and-down allocation technique. The ED50 and ED95 were calculated using a sequential formula and probit regression. Probit regression was also used to assess the relative potency of remimazolam between groups. Sedation levels were evaluated using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale.

Results: The ED50 for remimazolam was significantly lower in Group R+F compared to Group R (p= 0.007). Probit regression estimated the ED50 and ED95 values for Group R+F at 4.878 mg (95% CI, 3.845–5.859) and 8.184 mg (95% CI, 6.636–13.546), respectively. In contrast, Group R demonstrated ED50 and ED95 values of 6.733 mg (95% CI, 5.533–8.068) and 11.298 mg (95% CI, 9.101–19.617), respectively.

Conclusion: This study provides compelling evidence that the administration of 1 μg/kg of fentanyl significantly reduces the required sedative dose of remimazolam by approximately 30% during induction in elderly patients. Importantly, the concomitant use of 1 μg/kg of fentanyl does not increase the risk of adverse effects such as hypotension, respiratory depression.

Keywords: remimazolam, fentanyl, effective dose, elderly

Introduction

Remimazolam, a novel ultrashort-acting benzodiazepine, is increasingly favored in general anesthesia due to its unique pharmacokinetic profile, lack of cumulative effects, and independence from liver or kidney function for metabolism.[1] Studies have highlighted its favorable hemodynamic profile compared to propofol, particularly in patients with ASA grade I or II, and its safe use in patients with ASA grade III[2,3] and in elderly populations.[4]

Despite its growing adoption, consensus on recommended loading doses of remimazolam remained uncertain, particularly in elderly patients.[5,6] Clinical recommendations for elderly patients vary widely; for instance, reported ED50 values ranged from 0.088 mg/kg to 0.061 mg/kg for patients aged 60–69 and 70–75 years, respectively, with corresponding ED95 values ranging from 0.09 mg/kg to 0.118 mg/kg.[7] Another study suggested optimal doses of 0.19–0.25 mg/kg and 0.14–0.19 mg/kg for patients aged 60–80 and >80 years, respectively.[8] Furthermore, all the mentioned above studies had not

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considered the impact of opioids on the effective dose of remimazolam. Opioids were known to decrease the effective dosage of sedatives in anesthesia practice, where combinations of hypnotic-sedative agents and opioids were common.

The relationship between hypnotic agents and opioids in influencing the depth of sedation remained debated. While some studies indicated analgesics may reduce the required dosage of sedatives,[9–12] others reported no significant effect during propofol infusion.[13,14] However, the impact of low-dose fentanyl on the effective dose of remimazolam in elderly patients has not been explored.

Therefore, our study aimed to elucidate the impact of fentanyl on the effective dose of remimazolam in elderly populations, aiming to ensure safe and effective sedation during elective surgical procedures.

Materials and Methods

Study Design

This study, approved by the Ethics Committee of Hangzhou Women's Hospital (IRB: 202204–03), was conducted in the operating room of Hangzhou Women's Hospital from May 15, 2022, to December 31, 2022. This study was conducted in accordance with the principles of the Declaration of Helsinki. The research involved sixty elderly female patients undergoing elective general anesthesia surgery, who provided written informed consent. This study was registered in the Chinese Clinical Trial Registry (ChiCTR2200059962).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Patients aged 65–80 years undergoing general anesthesia surgery; (2) ASA (American Society of Anesthesiologists) class I–III; (3) Body mass index (BMI) between 18 and 30 kg/m^2; (4) Signed an informed consent form, demonstrated willingness to participate in the experimental procedure, and voluntarily agreed to be a subject.

The exclusion criteria included: (1) Allergy to remimazolam or contraindication to its use; (2) Preoperative impaired consciousness or chronic pain managed with long-term analgesic use, psychiatric medications, or alcohol abuse; (3) Utilization of sedatives, antiemetics, anti-itch medications, or monoamine oxidase inhibitors, or antidepressants within 24 hours prior to the surgery; (4) Patients with tumor, serious cardio-cerebrovascular disease; (5) Those who do not agree to participate or are participating in other drug trials.

Randomization and Blinding

We randomly allocated patients in a 1:1 ratio to one of two groups to receive an initial dose of remimazolam (7.5 mg) with fentanyl (1 μg/kg), or receive remimazolam (7.5 mg) with an equivalent volume of saline. Randomization codes were created using computer-generated random numbers (Microsoft Excel, Microsoft Corporation, Redmond, WA) and placed into opaque, sealed, sequentially numbered envelopes by an assistant before the commencement of the study. Randomization was conducted by an independent researcher not involved in subsequent procedures.

The study drugs were prepared by an anesthesia nurse who had been given detailed instruction on the protocol and remained blinded to patient allocation. Fentanyl (1 μg/kg) or blank saline was diluted in a 10 mL syringe of identical specifications, and remimazolam was diluted in a 20 mL syringe of identical specifications, as per the study protocol.

An attending anesthesiologist, unaware of the specific study drug, administered the anesthetic to ensure blinding. Patients were also blinded to the specific medications administered. Data collection was performed by another independent anesthesiologist, blinded to group assignments. Additionally, group assignments for patients, surgeons, and data analysts were kept concealed.

Anesthesia Procedure

Sedative premedication before surgery was strictly prohibited. Upon entering the operating room, standard vital signs monitoring, including heart rate, noninvasive blood pressure, peripheral pulse oxygen saturation, and body temperature, was initiated. Invasive monitoring was performed based on clinical needs. Before anesthesia induction, 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 preoperative fluid bolus. Adequate mask oxygen inhalation was administered before induction.

Following the initial administration of 25% of the calculated remimazolam dose, a 10-second pause allowed assessment of patient comfort the during injection. After anesthesia induction, Bispectral Index (BIS) values and vital signs were continuously recorded over 5 minutes. Remimazolam administration adhered to protocol, with sedation levels assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S)[15] scale. This standardized anesthesia procedure ensures consistent data collection and analysis protocols.

Administration of Remimazolam

In Group R, the initial dose of remimazolam (Hengrui Pharmaceutical Co, Ltd, Jiangsu China) during anesthesia induction in each group was set at 7.5 mg. Subsequent doses for elderly patients were adjusted in 2.5 mg increments or decrements based on the response of the previous subject, using the up-down sequential allocation technique described, by Dixon and Massey.[16]

"Successful sedation" was defined as achieving a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of 0 within 5 minutes following intravenous remimazolam administration.[7] Successful sedation prompted a decrement of 2.5 mg for the subsequent patient in that group, while ineffective sedation directed an increment of 2.5 mg.

If the MOAA/S score remained ≥ 1 within the initial 5 minutes following intravenous remimazolam administration, sedation was deemed ineffective. In such cases, a rescue dose of propofol (1 mg/kg) was administered, with the option of repeating at 3-minute intervals until achieving an MOAA/S score of 0. Following effective sedation, intravenous analgesics and muscle relaxants were administered, and upon their effectiveness, a tracheal catheter or laryngeal mask was inserted. The success or failure of the intravenous dose for each patient was recorded and was made known to the anesthesia nurse responsible for preparing the study drugs who adjusted the dose as necessary for the next patient.

In Group F+R, following the administration of 1 μg/kg of fentanyl citrate (Yichang Renfu Pharmaceutical Co, Ltd, Hubei, China), an intravenous injection of 7.5 mg remimazolam was administered during a 1-minute interval. Subsequent dosing adjustments for elderly patients followed the same up-and-down sequential allocation technique as described for Group R by Dixon and Massey.

MOAA/S monitor

The Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score assessed sedation levels as follows: a score of 5 indicated the patient is fully awake and responds promptly to their name; a score of 4 indicated a sluggish response to their name; a score of 3 indicated response after repeated loud calls of their name; a score of 2 indicated response only to gentle shaking or pushing; a score of 1 indicated response only to pain stimulation (trapezius squeeze); and a score of 0 indicated no response to pain stimulation (trapezius squeeze).

"Successful sedation" is defined as achieving and maintaining a MOAA/S score of 0 (no respond to painful trapezius squeeze) within 5 minutes following intravenous remimazolam administration.

BIS (Bispectral index) values were continuously monitored using the Aspect Medical Systems A-2000 BIS monitor (Leiden, Netherlands, version 3.4). BIS values range from 0 to 100, with higher values indicating clearer consciousness and lower values indicating greater suppression of the cerebral cortex.

Respiratory depression was defined as a respiratory rate below 10 breaths per minute persisting for more than 1 minute and/or a decrease in SpO2 to less than 90%. In cases where SpO2 dropped below 90%, jaw support or pressure respiration via face mask was administered.[5] Hypotension was characterized by a mean arterial pressure (MAP) below 65 mmHg following anesthesia induction.[17] Deoxyepinephrine (50 mg) was administered intravenously to manage hypotension, with repeated doses as necessary. Bradycardia, defined as a heart rate below 50 beats per minute, was treated with 0.5 mg of intravenous atropine. All additional adverse effects, such as hiccups, coughing, or intraoperative awareness, were meticulously documented.

Outcome measures and vital signs were documented both prior to and at specific time intervals following intravenous remimazolam administration, including at 1 minute (T1), 2 minutes (T2), 3 minutes (T3), 4 minutes (T4), and 5 minutes (T5). This robust protocol ensures thorough monitoring and documentation for comprehensive analysis.

Primary Outcome

The primary objective of this study was to assess the efficacy of remimazolam sedation, with or without fentanyl, at the 5-minute mark using the MOAA/S monitor.[7]

Alongside this primary outcome, various other perioperative outcomes were also assessed.

Sample Size

A sample size of 30 subjects per group was determined based on recommendations suggesting that 20–40 subjects per group provide a stable estimate of the ED50 using the Dixon up-down method.[18,19] Additionally, calculations from our preliminary pilot data indicated that having ≥23 subjects per group would yield ≥90% power to detect a 20% difference in ED50 values for remimazolam between groups at an alpha level of 0.05.

To accommodate potential dropouts (estimated at 20%) and to achieve narrower confidence intervals, a total of 60 subjects were enrolled in the study, evenly distributed with 30 subjects in each group.

Statistical Analysis

Continuous data normality was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables, such as patients' demographic data, were presented as means±SD and analyzed for significance using one-way analysis of variance (ANOVA). Variables with non-normal distribution were presented as the median and interquartile range (IQR) and analyzed using the Mann–Whitney *U*-test. Post hoc Bonferroni test was employed for pairwise comparisons. Categorical variables were presented as absolute numbers and percentages.

The ED50 values of remimazolam were determined by calculating the mean of the midpoints of pairs of remimazolam doses administered in successive patients, where a case of ineffective sedation was followed by a case of effective sedation, or vice versa (turning points), using the modified up-and-down allocation method.[20–22] The 95% CI and SD for the ED50 values were calculated following the method suggested by Choi.[22] Probit regression analysis was utilized as a backup and sensitivity test, analyzing tallied numbers of effective and ineffective sedation for each dose category in each group.[18] Estimates of the ED50 for remimazolam in each group were obtained, and the difference between the two groups was quantified by calculating the relative mean potency with a 95% CI, as previously described.[23] This comprehensive statistical analysis ensures robust and reliable findings from the study.

Results

Initially, 69 patients were recruited for the study, with seven excluded for not meeting inclusion criteria and two declining to participate. The Consolidated Standards of Reporting Trials (CONSORT) diagram, depicted in Figure 1, illustrates the study flow. Subsequently, the final analysis was conducted on a cohort of 60 patients. Demographic data and sedation indices (MOAA/S and BIS value) revealed no significant differences among the groups, as detailed in Table 1.

Age did not differ significantly between Group R and Group F+R (69.8±7.7 vs 70.6±5.4, $p > 0.05$). Similarly, there were no significant differences in BMI between the groups during anesthetic induction (23.2±3.4 vs 24.0±2.9, $p > 0.05$). The composition ratio of the ASA classification of anesthesia also showed no significant difference between the two groups ($p > 0.05$) (Table 1).

The ED 50 and ED 95 Sedative Dose of Remimazolam-Induced

The ED50 and ED95 for the sedative dose of remimazolam-induced anesthesia are illustrated in the up-down sequences shown in Figures 2, and the determined ED50 for remimazolam exhibited a lower value in Group F+R compared to Group R ($p = 0.007$). Dose-response curves derived from probit regression analysis are presented in Figure 3. Utilizing probit regression, the calculated ED50 and ED95 values for Group F+R were 4.878 mg (95% CI, 3.845–5.859) and 8.184 mg (95% CI, 6.636–13.546), respectively. In contrast, Group R demonstrated ED50 and ED95 values of 6.733 mg (95% CI, 5.533–8.068) and 11.298 mg (95% CI, 9.101–19.617), respectively. The estimate of relative mean potency for remimazolam in Group F+R vs Group R was 0.72 (95% CI, 0.37–0.96).

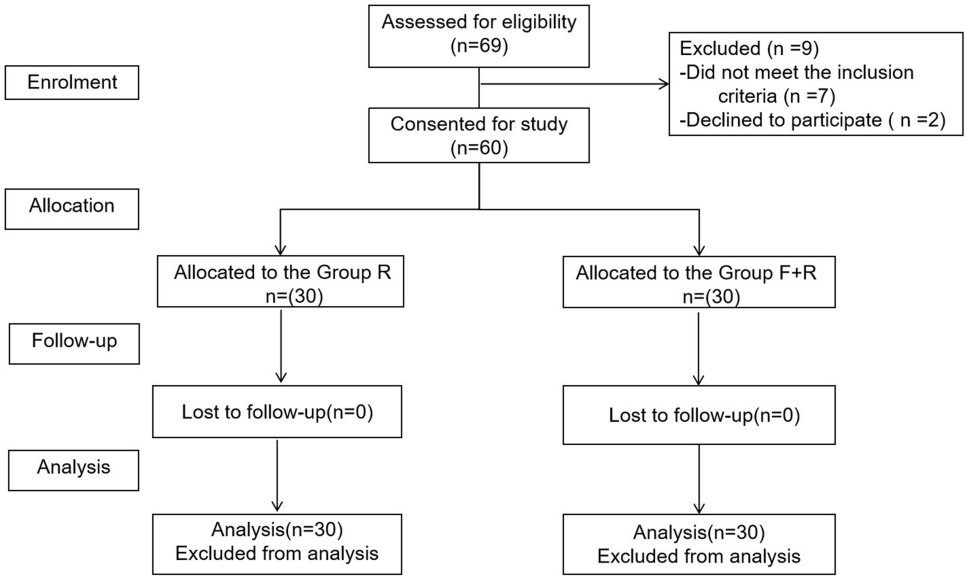

Figure 1 CONSORT flow diagram.

Perioperative adverse events are summarized in Table 2. All patients in both groups experienced no intraoperative awareness. There were no significant differences between the groups in the incidence of hypotension, bradycardia, injection pain, hiccups, or respiratory depression during the first 5 minutes after the induction of general anesthesia ($p>0.05$) (Table 2).

Discussion

In this dose-response study, we evaluated and compared the ED50 and ED95 values of intravenous remimazolam for induced sedation in elderly patients, both with and without fentanyl. Notably, our findings indicated that the administration of 1 μg/kg of fentanyl significantly reduces the required sedative dose of remimazolam by approximately 30% during the remimazolam-induction process in elderly patients, and the calculated ED50 and ED95 values were 4.878 mg (95% CI, 3.845–5.859) and 8.184 mg (95% CI, 6.636–13.546), respectively. Importantly, the concomitant use of 1 μg/kg of fentanyl does not increase the risk of adverse effects such as hypotension, respiratory depression.

The strength of this study lies in its comprehensive determination of the dose-response curve of intravenous remimazolam for induced sedation in elderly patients, both with and without fentanyl. Additionally, the inclusion of a dose-response curve

Table 1 Main Characteristics and Sedation Index

	Group R *n*=30	Group F+R *n*=30	*P*
Age, y	69.8±7.7	70.6±5.4	0.658
Weight, kg	60.0±9.8	60.1±7.8	0.987
Height, cm	160.4±6.5	158.0±4.1	0.096
BMI (kgm $^{-2}$)	23.2±3.4	24.0±2.9	0.316
ASA classification, n (%)			0.786
I	3(10%)	2(6.67%)	
II	24(80%)	26(86.67%)	
III	3(10%)	2(6.67%)	
BIS value	66.23±11.04	68.20±11.09	0.484
MOAA/S score	0.5(0,1.25)	1(0,3)	0.476

Notes: Data are expressed as M ± SD, median (interquartile range), or number (%).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists status; BIS value, Bispectral index value.

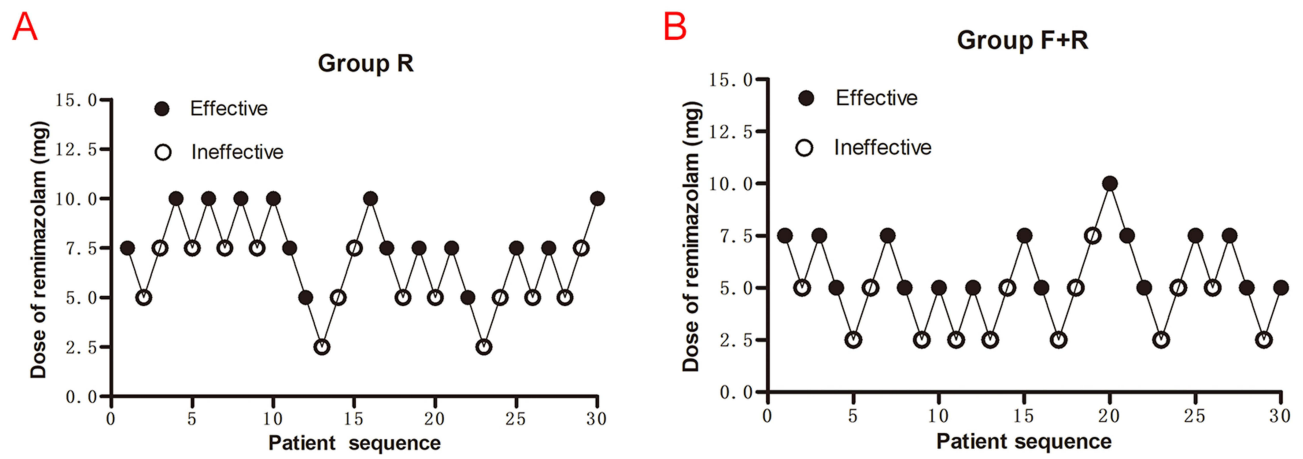

Figure 2 Individual response to intravenous remimazolam at a corresponding dose (mg), (**A**) for Group R of receiving remimazolam alone and (**B**) for Group F+R of receiving an initial dose of remimazolam with fentanyl.

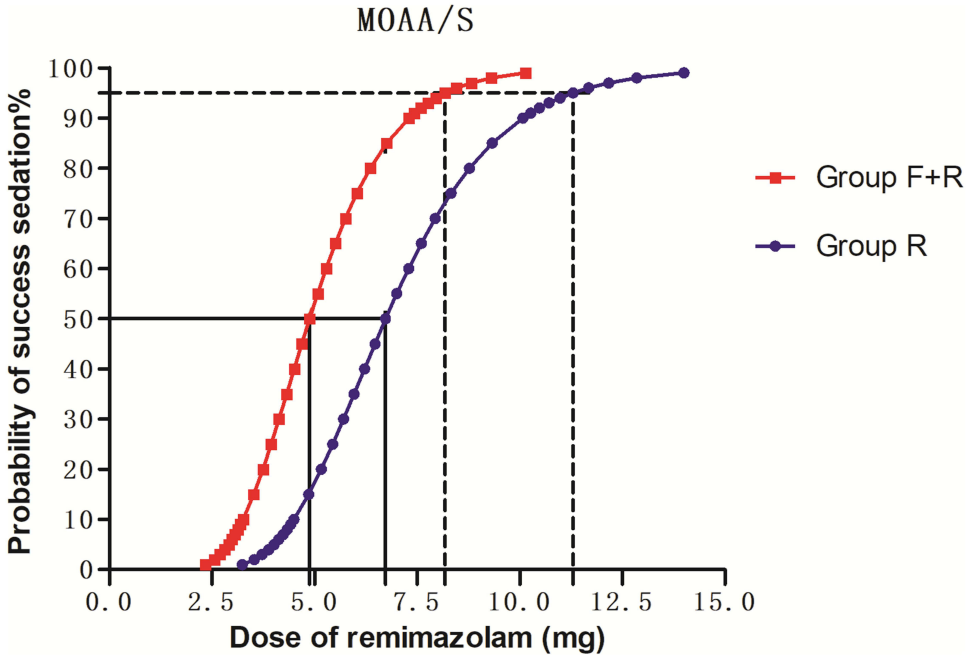

Figure 3 Dose-response curves of intravenous remimazolam for anesthesia sedation plotted from estimated probabilities of effective response (1 to 100%) vs the corresponding dose of the initial bolus derived from probit regression analysis. Utilizing probit regression, the calculated ED50 and ED95 values for Group F+R were 4.878 mg (95% CI, 3.845–5.859) and 8.184 mg (95% CI, 6.636–13.546), respectively. In contrast, Group R demonstrated ED50 and ED95 values of 6.733 mg (95% CI, 5.533–8.068) and 11.298 mg (95% CI, 9.101–19.617), respectively. Solid lines represent the ED 50 values and dashed lines represent the ED 95 values.

provides valuable insights for healthcare providers. Notably, as previous studies on remimazolam doses in elderly patients did not consider the concurrent use of fentanyl, our study contributes novel evidence supporting the utilization of remimazolam in geriatric populations. The integration of fentanyl in this study design adds a nuanced perspective to the existing literature and reinforces the potential efficacy and safety of remimazolam in the elderly patient demographic.

Although the optimal intravenous dose of remimazolam for induced sedation remains a subject of debate, there is a scarcity of research specifically addressing the dosing for elderly patients. In our up-and-down sequential allocation study, we observed a significant reduction, approximately 30%, in the median effective dose of remimazolam-induced sedation in elderly female patients during anesthetic induction when fentanyl was administered. The ED95 values for remimazolam-induced sedation in elderly patients were 0.117 [0.095–0.194] mg/kg with fentanyl and 0.161 [0.130–0.280] mg/kg without

Table 2 Adverse Events

	Group R *n*=30	Group F+R *n*=30	*P*
Hypotension (%)	1(3.33%)	2(6.67%)	>0.99
Bradycardia (%)	0(0%)	2(6.66%)	0.492
Injection pain (%)	2(6.67%)	1(3.33%)	0.637
Hiccups (%)	3(10%)	2(6.67%)	>0.99
Respiratory depression (%)	11(36.67%)	13(43.33%)	0.598
Intraoperative awareness (%)	0(0%)	0(0%)	>0.99

Notes: Data are expressed as number (%).

fentanyl (1 μg/kg) after conversion during anesthetic induction. A recent study[7] investigating remimazolam for anesthesia induction in elderly patients found ED95 values of 0.118 mg/kg (95% CI, 0.103–0.649) and 0.090 mg/kg (95% CI, 0.075–0.199) in groups aged 60–69 years and 70–85 years, respectively, based on MOAA/S score assessments. The concordance between our study's findings and theirs suggests consistency in the criteria for effective sedation.

In another study,[8] optimal doses of 0.25–0.33, 0.19–0.25, and 0.14–0.19 mg/kg were proposed for achieving loss of consciousness (LoC) in patients aged <40, 60–80, and >80 years, respectively, without the inclusion of analgesics. Notably, the ED95 value of remimazolam without fentanyl was close to those in the 60–80 years group from the above study, suggesting a similar trend, possibly due to the absence of analgesics. However, the ED95 of concomitant use of fentanyl and remimazolam was significantly lower, likely attributed to the synergistic effect of fentanyl. Our findings underscore that fentanyl administration substantially reduces the effective dose of remimazolam by approximately 30%, aligning with the conventional belief that opioids enhance the anesthetic effect of sedatives.[11,24]

The consistency in the ED50 findings derived from the two statistical approaches, sequential method and probit regression analysis, in our study enhances the reliability of our data (Supplementary Table 1). These results are anticipated to provide valuable information for the effective use of remimazolam in inducing general anesthesia in elderly patients. Previous studies[9] have shown that opioids, beyond their analgesic properties, induce a sedative state with electrocortical patterns resembling anesthesia or sleep. Beyond their analgesic properties, opioids are known to induce a profound sedative state and elicit electrocortical patterns resembling reduced brain arousal, akin to anesthesia or sleep.[25,26] Additionally, prior research[27,28] has illustrated that fentanyl reduces behavioral activity, decreases the fragmentation of sleep-wake states, minimizes the occurrence of brief electrocortical arousals, and eliminates REM (Rapid Eye Movement sleep), all of which are consistent with a state of sedation. Fentanyl, specifically, has been demonstrated to induce dose-dependent changes in electroencephalogram (EEG) activity, with lower doses affecting high-frequency β power and increasing α activity.[25]

While BIS monitoring is widely used for gauging the depth of sedation, primarily designed for propofol and focusing on the beta band. Remimazolam acts on gamma-aminobutyric acid (GABA) receptors, and EEG changes during its sedation show higher signal-to-noise ratios in the alpha band compared to the beta band.[29] MOAA/S values have been widely utilized in previous studies to assess the effective dose of remimazolam.[30] Due to its stable baseline readings and graded response aligning with sedative effects, MOAA/S is considered highly suitable for monitoring sedation levels during remimazolam administration. However, in a recent study, it had been proven that the BIS showed an acceptable correlation with the effect-site remimazolam concentration and depth of sedation, suggesting that this EEG-derived parameter is a potentially reliable hypnotic indicator during remimazolam sedation. The recommended ED95 dose for remimazolam-induced sedation in our study was determined to be 8.184 mg when assessed using MOAA/S scores, particularly relevant when low-dose fentanyl is administered.

No patients in this study experienced severe hypotension necessitating treatment with inotropics or vasopressors. The maximal decrease in systolic blood pressure (SBP) occurred at 5 minutes after the administration of the remimazolam bolus injection. Previous research has indicated that continuous remimazolam infusion does not result in clinically significant hemodynamic instability.[8]

Our study had several limitations. First, patients greater than 80 years of age were not explored in this study, and super-elderly patients are a direction for further research in the future. Furthermore, it was carried out exclusively on a female population, and therefore the results may not be applicable to men. Moreover, it may be more accurate to assess the sedative effects of drugs using the Bispectral Index (BIS) rather than the MOAA/S scale. A recent study has suggested that this EEG-derived parameter is a potentially reliable indicator of hypnosis during remimazolam sedation. Finally, the study was limited to the relatively healthy elderly patients undergoing elective surgeries. Further research must focus on highly at risk elderly people.

Conclusions

In conclusion, fentanyl administration significantly lower the median effective dose of remimazolam-induced sedation by about 30% in elderly female patients during anesthetic induction. Importantly, the concomitant use of 1 μg/kg of fentanyl does not increase the risk of adverse effects such as hypotension, respiratory depression. The ED 95 of remimazolam-induced sedation for elderly patient were respectively 8.184 mg and 11.298 mg with or without fentanyl (1ug/kg) during anesthetic induction.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by The Ethics Committee of Hangzhou Women's Hospital (IRB: 202204-03) and written informed consent was obtained from all subjects participating in the study.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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