

Isobolographic Analysis of the Interaction Between Remimazolam and Etomidate in General Anesthesia Induction: A Prospective, Sequential Allocation Study Based on the Dixon Up-and-Down Method

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Purpose: This study aimed to investigate the sedative interaction between the new benzodiazepine derivative remimazolam and etomidate during general anesthesia induction and determine the appropriate dose ratio for their combined use.

Patients and Methods: Patients scheduled for general anesthesia, aged 18 to 60 years with a BMI of 18 to 28 kg/m² and American Society of Anesthesiologists (ASA) physical status I–II, were randomly divided into five groups using a random number table. The modified Dixon up-and-down method was employed to determine the median effective dose (ED₅₀) of remimazolam in Group A (remimazolam group) and etomidate in Group B (etomidate group). For the combined medication groups: Group C (0.25 ED₅₀ remimazolam + 0.75 ED₅₀ etomidate), Group D (0.5 ED₅₀ remimazolam + 0.5 ED₅₀ etomidate), and Group E (0.75 ED₅₀ remimazolam + 0.25 ED₅₀ etomidate), the dose of remimazolam was fixed in each group, and the ED₅₀ of etomidate in each group was calculated. Isobolographic analysis was utilized to assess the sedative interaction between the two drugs, and the interaction index and optimal dose ratio for synergism were calculated.

Results: The ED₅₀ of remimazolam and its 95% confidence interval (95% CI) in Group A were 0.193 (0.167–0.253) mg/kg, while those of etomidate in Group B were 0.155 (0.118–0.20) mg/kg. Isobolographic analysis revealed remimazolam and etomidate produced a synergistic effect in Groups C and D, and an additive effect in Group E. When combined at 0.048 mg/kg remimazolam and 0.062 mg/kg etomidate, the optimal dose ratio for the strongest synergism was 1:1.29.

Conclusion: During general anesthesia induction, when the dose ratios of remimazolam to etomidate are approximately 1:1.29 and 1:0.39, the two drugs exert a synergistic sedative effect, with the strongest synergism observed at the dose ratio of 1:1.29.

Keywords: isobolographic analysis, drug-drug interaction, remimazolam, etomidate

Introduction

During anesthesia induction, single-agent sedation typically requires higher doses, leading to hemodynamic depression.^{1,2} Combining anesthetics may reduce drug dosages and associated adverse reactions while enhancing cardiovascular stability.³ Remimazolam is a new benzodiazepine derivative drug that can alleviate preoperative anxiety in patients.⁴ Compared with traditional sedatives, remimazolam exhibits superior hemodynamic stability and can be



antagonized by flumazenil.⁵ However, its sedation success rate is lower than that of propofol.⁶ Etomidate is a non-barbiturate intravenous general anesthetic that provides adequate sedation depth and stable hemodynamics during induction,⁷ but it is associated with a high incidence of myoclonus and convulsions.

Isobolographic analysis is a simple and accurate method for evaluating drug interactions, enabling quantitative confirmation of changes in drug effects after combined administration.⁸ This study used isobolographic analysis to explore the interaction between remimazolam and etomidate, providing a rational reference for clinical medication.

Materials and Methods

Inclusion and Exclusion Criteria

Eligible patients were those undergoing elective surgery under general anesthesia, of any gender, aged 18–60 years, with ASA physical status I–II and a BMI of 18–28 kg/m².

Exclusion criteria included: hypersensitivity to remimazolam or etomidate; pregnancy or lactation; severe cardiovascular diseases; chronic alcoholism; patients unfit for elective surgery; use of sedatives or opioids within 24 hours; severe mental illness; and myasthenia gravis.

Sample Size Calculation

The Dixon up-and-down method can effectively reduce the number of subjects required for a study. Its sample size is not determined by traditional power analysis but by a predefined stopping rule.⁹ When this method is adopted, the type of experiment does not influence the calculation of sample size. A stable and reliable estimate of the median effective dose (ED₅₀) can be achieved when at least six crossover points are observed—defined as a transition from a positive response to a negative response, or vice versa.¹⁰ To ensure statistical robustness, this study pre-specified that after the first crossover point was observed, subject enrollment would continue until a total of seven crossover points were recorded, which served as the trial termination criterion. Thus, the sample size was determined sequentially rather than as a fixed pre-calculated value.

Ethics

This was a prospective, sequential allocation study based on the Dixon up-and-down method. A total of 135 patients who underwent general anesthesia at the Second Hospital of Shanxi Medical University during the period from June 19 to July 19, 2025, were enrolled in the present study. It was approved by the Ethics Committee of the Second Hospital of Shanxi Medical University (Approval No.: [2025] YX No. 208, Approval Date: June 3, 2025) and registered at ClinicalTrials.gov (NCT07012902, Registration Date: June 8, 2025). Written informed consent was obtained from all patients and their family members. The study adhered to the principles of the Declaration of Helsinki.

Grouping and Intervention

The experiment was divided into two phases. In Phase 1, patients were randomly divided into two groups using a random number table: Group A (remimazolam group) and Group B (etomidate group). The initial doses of remimazolam in Group A¹¹ and etomidate in Group B¹² were 0.2 mg/kg and 0.12 mg/kg, respectively, with adjacent dose ratios of 1:0.8 and 1:0.6. The ED₅₀ values of Group A and Group B were calculated using the Dixon up-and-down method.¹³ In Phase 2, the calculated ED₅₀ values of remimazolam and etomidate were used as the initial doses for the subgroups. Patients were randomly divided into three combined medication groups using a random number table: Group C (0.25 ED₅₀ remimazolam + 0.75 ED₅₀ etomidate), Group D (0.5 ED₅₀ remimazolam + 0.5 ED₅₀ etomidate), and Group E (0.75 ED₅₀ remimazolam + 0.25 ED₅₀ etomidate). The dose of remimazolam was fixed in each group, and the ED₅₀ of etomidate in Groups C, D, and E was calculated using the modified Dixon up-and-down method.

Anesthesia Method and Observation Indicators

All patients fasted for 8 hours and abstained from water for 2 hours preoperatively; and no special preoperative medications were administered. Upon entering the operating room, blood pressure, heart rate, oxygen saturation, and

bispectral index (BIS) were monitored, and oxygen was administered via face mask at 5 L/min. After triple verification, an intravenous access was established in the upper limb for fluid infusion, followed by anesthesia induction. Remimazolam (Bath: 250727AP, Hengrui Pharmaceutical, Jiangsu, China) was diluted with 0.9% sodium chloride solution to 2 mg/mL, and etomidate (Bath: TVT25D11, Enhuai Pharmaceutical, Jiangsu, China) was administered by slow intravenous injection directly. According to the dose of each group, remimazolam and etomidate were injected over no more than 10 seconds. For combined medication, the two drugs were injected with an interval of more than 10 seconds, and the infusion tube was flushed with 5 mL of normal saline after the injection of each drug. Evaluation was performed 1 minute after the completion of injection. A positive response, indicating successful sedation, was defined as a BIS value of 45–60¹⁴ and a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score ≤ 1 .¹⁵ For a positive response, the dose was reduced by one gradient for the next patient; otherwise, the dose was increased by one gradient. Observation in Phase 1 ended when the 7th crossover (from positive to negative response) was observed after the first crossover. If the patient showed a negative response, 0.05 mg/kg of remimazolam or etomidate was added for rescue sedation. If the patient showed a positive response, sufentanil (Bath: AB5950700821, Renfu Pharmaceutical, Hubei, China) 0.45 $\mu\text{g}/\text{kg}$ and rocuronium (Bath: 251202, Fuan Pharmaceutical, Hubei, Chongqing, China) 0.6 mg/kg were administered sequentially, followed by controlled ventilation. After mask ventilation with positive pressure for 3 minutes, tracheal intubation and mechanical ventilation were performed, and then the surgical procedure was carried out.

The incidence of adverse reactions including myoclonus and hiccups was recorded in each subgroup.

Statistical Analysis

The Shapiro–Wilk test was used to assess the normality of continuous data. Normally distributed data were expressed as mean \pm standard deviation ($\bar{x} \pm s$), while skewed data were expressed as median (interquartile range, IQR).

The unit of analysis was the individual patient, and all observations were independent. All data were analyzed using SPSS 27.0. For intergroup comparisons, normally distributed data were analyzed using one-way analysis of variance (ANOVA). Before performing ANOVA, the Levene test was used to assess the homogeneity of variances. If the variances were homogeneous ($P > 0.05$), standard ANOVA was applied; if the variances were heterogeneous ($P < 0.05$), Welch's ANOVA was used as a correction. Skewed Data were analyzed using the Kruskal–Wallis test. Categorical variables were compared between groups using the chi-square test. A P value < 0.05 was considered statistically significant.

The ED_{50} and its 95% CI for each group were calculated using the Probit method in SPSS 27.0, with non-overlapping CIs being interpreted as statistically significant.

Isobolograms were drawn to reflect the results of the isobolographic analysis. The ED_{50} and its 95% CI of etomidate in Group B were plotted on the abscissa, and the ED_{50} and its 95% CI of remimazolam in Group A were plotted on the ordinate. The line connecting the two ED_{50} values constituted the additive line, and the line connecting the 95% confidence limits of the two ED_{50} values constituted the 95% confidence region. The interaction was judged according to the position of the combination point: points to the left and outside the confidence region indicated synergy, points inside indicated additivity, and points to the right and outside the confidence region indicated antagonism. GraphPad Prism 9.0 software was used to draw the sequential plots of ED_{50} and isobolograms for each group.

The interaction index (R) was used to evaluate the intensity of drug interaction, where $R = 1$, $R > 1$, and $R < 1$ represented additive, synergistic, and antagonistic effects, respectively. The larger the R value, the stronger the synergistic effect. The interaction index values (R) for Groups C, D, and E were calculated by algebraic analysis, as shown in the following formula:

$$\text{interaction index (R)} = 1 / \left(\frac{\text{Actual dose of Remimazolam}}{\text{ED}_{50} \text{ of Remimazolam}} + \frac{\text{Actual dose of Etomidate}}{\text{ED}_{50} \text{ of Etomidate}} \right)$$

Results

A total of 135 patients were enrolled and randomly assigned to Groups A, B, C, D, and E. Comparisons of age, BMI, and Sex among the five groups are presented in Table 1.

Table 1 Comparison of General Information Among Five Groups

Characteristics	Group A (n=24)	Group B (n=24)	Group C (n=32)	Group D (n=25)	Group E (n=30)	Statistical Values	P-value
Sex						$\chi^2=4.098$	0.401
Male	8 (33.3%)	10 (41.7%)	18 (56.3%)	10 (40%)	16 (53.9%)		
Female	16 (66.7%)	14 (58.3%)	14 (43.8%)	15 (60%)	14 (46.7%)		
Age	39±11	41±11	41±11	40±13	42±12	F=0.242	0.914
BMI	23.6±2.8	24.4±2.2	23.8±2.9	23.1±3.1	23.6±4.8	F=0.434	0.784

Age and BMI met the assumptions of normality and homogeneity of variance. ANOVA showed no statistically significant differences in age ($F = 0.242$, $P = 0.914$) or BMI ($F = 0.434$, $P = 0.784$) among the five groups. No post-hoc pairwise comparisons were performed following ANOVA. The chi-square test revealed no statistically significant difference in sex distribution among the five groups ($\chi^2 = 4.098$, $P = 0.401$).

The ED₅₀ (95% CI) of remimazolam for sedation in Group A was 0.193 (0.167–0.253) mg/kg, with the sequential plot shown in Figure 1. The ED₅₀ (95% CI) of etomidate for sedation in Group B was 0.155 (0.118–0.20) mg/kg, with the sequential plot shown in Figure 2. For combined medication: in Group C, the initial dose of remimazolam was 25% of its ED₅₀ (0.048 mg/kg) and that of etomidate was 75% of its ED₅₀; the ED₅₀ (95% CI) of etomidate for sedation in Group C was 0.062 (0.047–0.082) mg/kg calculated by the Probit method. In Group D, the initial dose of remimazolam was 50% of its ED₅₀ (0.096 mg/kg) and that of etomidate was 50% of its ED₅₀; the ED₅₀ (95% CI) of etomidate for sedation in Group D was 0.037 (0.021–0.061) mg/kg. In Group E, the initial dose of remimazolam was 75% of its ED₅₀ (0.147 mg/kg) and that of etomidate was 25% of its ED₅₀; the ED₅₀ (95% CI) of etomidate for sedation in Group E was 0.019 (0.013–0.025) mg/kg. The sequential plots of Groups C, D, and E are shown in Figure 3.

Isobolographic analysis showed that Groups C and D exhibited synergistic effects, while Group E exhibited an additive effect, as shown in Figure 4.

Through algebraic analysis, the interaction indices for the three groups were 1.54, 1.36, and 1.13. Although the calculated value of R for Group E was >1, its 95% CI included 1, so isobolographic analysis classified Group E as additive.

When the doses of remimazolam and etomidate were set at 0.048 mg/kg and 0.062 mg/kg, respectively, the interaction index of the combined administration reached the maximum value, with the strongest synergistic effect

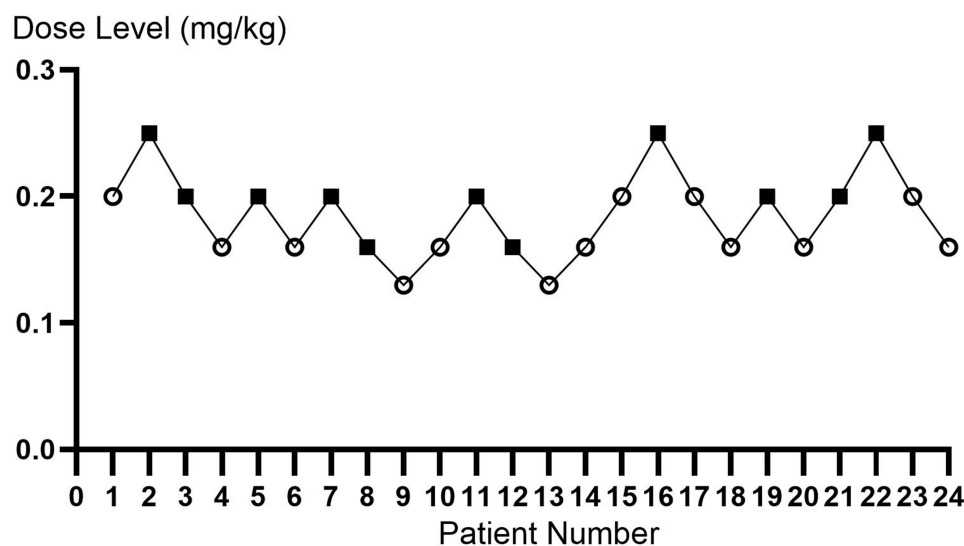


Figure 1 Sequential plot of Group A. Solid black square represents the positive dose; white circle represents the negative dose.

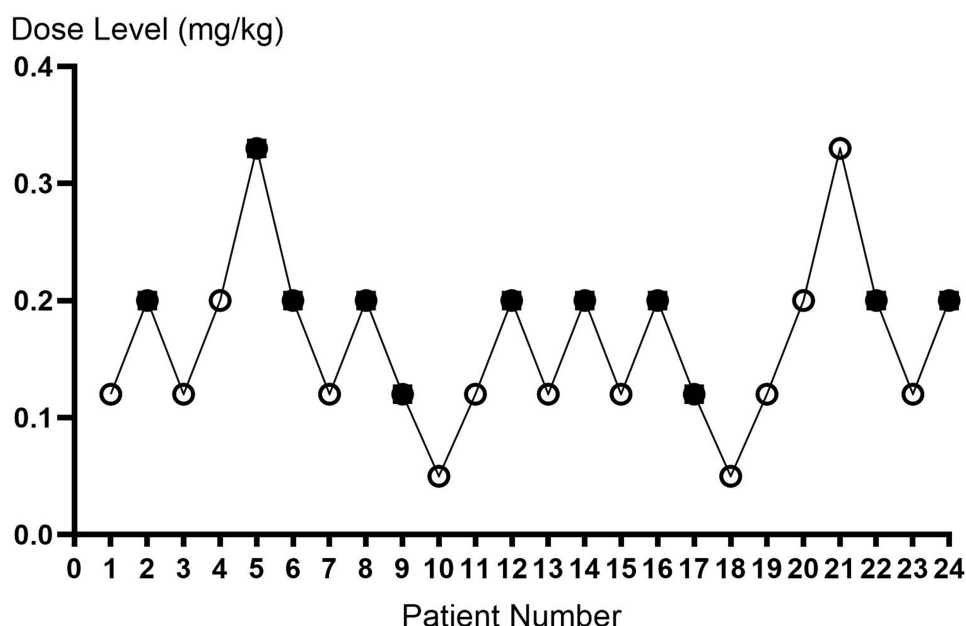


Figure 2 Sequential plot of Group B. Solid black square represents the positive dose; white circle represents the negative dose.

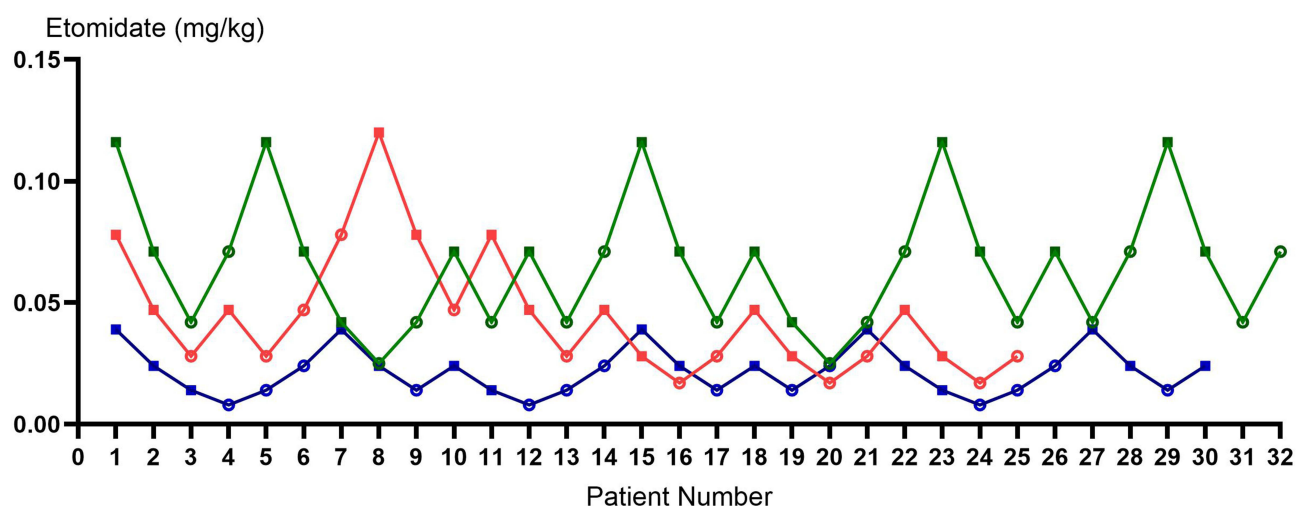


Figure 3 Sequential plots of Group C, D, E Green line: Group C; red line: Group D; blue line: Group E.

observed; accordingly, the optimal dose ratio of remimazolam to etomidate was approximately 1:1.29 (remimazolam: etomidate).

One case of hiccup was observed in Group A, and two cases of myoclonus were observed in Group B. No adverse reactions of remimazolam or etomidate were observed in Groups C, D, and E where remimazolam was administered first.

Discussion

Isobolographic analysis is a commonly used and accurate method for evaluating drug interactions.¹⁶ This method first measures the median effective dose of each drug for a specific effect, marks them on the X-axis and Y-axis (representing the potency of the two drugs, respectively), then connects the two single-agent ED₅₀ values to draw a straight line. The type of interaction between them can be accurately determined based on the position of the dose required to achieve the “median effect” (acting on 50% of patients) after combined administration of the two drugs on the isoblogram. If the effect point after combined administration of the two drugs lies on the line connecting the two drugs, it indicates an

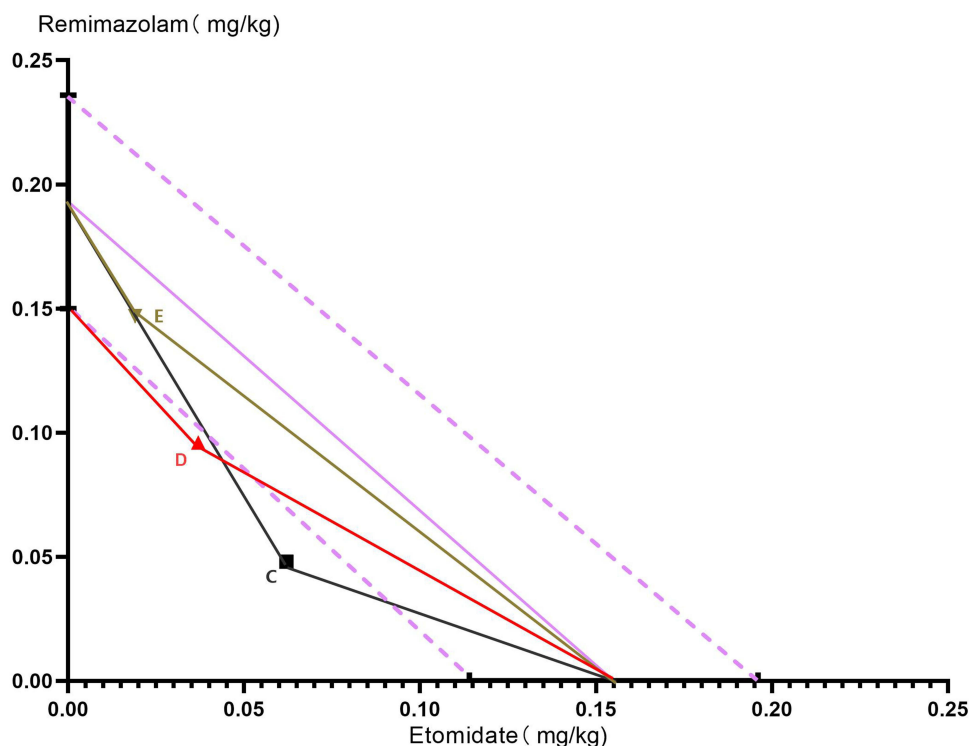


Figure 4 Isobologram. Solid purple line: additive isobole; dashed purple line: 95% CI; Solid black square: experimental interaction line of Group C; solid red upright triangle: experimental interaction line of Group D; brown inverted triangle: experimental interaction line of Group E.

additive effect of the two drugs; if the effect point lies below and to the left of the line, it indicates a synergistic effect; if the effect point lies above and to the right of the line, it indicates an antagonistic effect. This study employed three distinct dose combinations of the two drugs. The results showed that the ED_{50} intersection points of Groups C and D were to the left of the isobologram line and the 95% confidence interval, suggesting that these two drug dose combinations exhibited synergistic effects, while the ED_{50} intersection point of Group E was within the isobologram line and its 95% confidence interval, suggesting that this drug dose combination exhibited an additive effect.

Synergism is defined as the combined effect of clinical drugs that substantially exceeds the sum of their individual effects,¹⁶ and the interaction index represents the degree of synergism.¹⁷ In the present study, the interaction index R was used, where $R > 1$ indicates synergy and a larger R corresponds to a stronger synergistic effect. Among the three subgroups, Group C had the strongest synergistic effect, indicating that when the dose ratio of remimazolam to etomidate was approximately 1:1.29, the side effects were minimal and the combination was most suitable for clinical application.

BIS was initially developed and validated based on propofol, and its application in benzodiazepines has been questioned.^{18,19} BIS has a strong dose correlation with anesthetics such as propofol,²⁰ but a weak dose correlation with remimazolam.²¹ Administration of remimazolam can induce frontal β -wave activation, which may result in relatively high BIS values in some patients even with adequate sedation.²² Unlike other commonly used intravenous anesthetics, the magnitude of BIS values is not entirely equivalent to the depth of anesthesia.¹⁸ The sedation-alertness index is evaluated based on the patient's actual behavioral responses, which is less affected by individual physiological differences,¹⁵ and there is a strong positive correlation between BIS and OAA/S in the use of benzodiazepines.²³ Their combined use can integrate electroencephalographic signals and behavioral states, reducing evaluation errors caused by individual differences.

Etomidate alone has a high incidence of myoclonus and convulsions. Literature reports that the incidence of myoclonus during etomidate induction is 50–80% in patients without preoperative sedation, while the use of sedatives can reduce the incidence to 25%.²⁴ Remimazolam can reduce etomidate-induced myoclonus.²⁵ As early as 1992, it was known that preoperative use of low-dose sedatives can reduce the incidence of etomidate-induced myoclonus.²⁶ In this

study, low-dose remimazolam was administered first for sedation in Groups C, D, and E, which significantly reduced the incidence of etomidate-induced myoclonus.

Chen et al performed isobolographic analysis and demonstrated that etomidate and midazolam exhibited an additive hypnotic effect at a dose ratio of 2:1.²⁷ In the present study, the dose ratios of remimazolam to etomidate were 1:1.29 in Group C, 1:0.39 in Group D, and 1:0.129 in Group E, which showed synergistic, synergistic, and additive effects, respectively. This indicates that the differential drug interactions seen in this study may be related to the predetermined dose of remimazolam.

Both remimazolam and etomidate target the GABAA receptor as the core. However, they act on distinct subunits.²⁸ The molecular structure of remimazolam contains a benzodiazepine ring, which can bind to the extracellular domain interface between the α subunit and γ subunit of the GABAA receptor. After binding, the side chain of the molecule can form hydrogen bonds and hydrophobic interactions with the amino acid residues of the receptor subunit, inducing conformational changes in the receptor. This conformational regulation does not directly open the chloride channel, but enhances the affinity of endogenous GABA for the receptor binding site, improves the efficiency of GABA-mediated channel activation, and ultimately indirectly promotes chloride ion influx, enhancing the central inhibitory effect.²⁹ The etomidate molecule contains an imidazole ring and an ester group, and its active conformation can accurately embed the extracellular-transmembrane junction zone of the $\beta 2/\beta 3$ subunit of the GABAA receptor. This site does not overlap with the BZ site and is spatially independent. After binding, the etomidate molecule can form specific interactions with key amino acid residues of the β subunit, directly stabilizing the activated conformation of the receptor, prolonging the opening time of the chloride channel without relying on endogenous GABA, significantly increasing the total influx of chloride ions, and producing a potent sedative-anesthetic effect.³⁰

Population pharmacokinetic/pharmacodynamic (PK/PD) modeling of remimazolam for general anesthesia induction and population PK/PD modeling of short-term etomidate infusion in healthy volunteers have both shown that the dose-effect relationships of the two drugs conform to the E-max model,^{31,32} suggesting that the binding sites of GABAA receptors are limited.

We hypothesize that under sub-saturating conditions at GABAA receptors, remimazolam increases the channel opening frequency, while etomidate prolongs the mean open duration. By independently modulating these two distinct kinetic parameters, the drugs produce a molecular-level superposition of effects. This synergy significantly enhances total chloride influx per unit time, thereby intensifying neuronal membrane hyperpolarization and amplifying central inhibition. Crucially, since neither agent has reached receptor saturation, this synergistic potentiation operates below the ceiling effect imposed by limited receptor availability.

However, when a higher concentration of remimazolam is administered first, although the binding sites of the two are independent, there may be molecular-level spatial conflicts between the receptor conformations induced by the two. The GABAA receptor has saturation. It is speculated that after high-concentration remimazolam occupies most of the α - γ interface sites, even if etomidate binds to the unsaturated β subunits, the corresponding receptors may not form effective activation due to the binding of remimazolam, thus showing a simple additive effect. However, this speculation needs to be confirmed by more subsequent studies.

This study has the following limitations: (1) it is a single-center study; (2) only the effects near ED₅₀ were studied; (3) BIS and sedation-alertness scores are only observational indicators of clinical anesthesia, and the interaction between other clinical endpoints needs further research. Studying multi-drug combination strategies has more advantages in clinical work. The combined application of BIS and sedation-alertness scores make the outcomes more accurate, and observing the incidence of adverse reactions greatly increases clinical applicability.

Conclusion

During general anesthesia induction, when the dose ratios of remimazolam to etomidate are approximately 1:1.29 and 1:0.39, the two drugs exert a synergistic sedative effect, with the strongest synergism observed at the dose ratio of 1:1.29.

Abbreviations

ASA, American Society of Anesthesiologists; BMI, Body Mass Index; ED₅₀ the median effective dose; 95% CI 95% confidence interval; BIS bispectral index; MOAA/S Modified Observer's Assessment of Alertness/Sedation.

Data Sharing Statement

De-identified individual participant data, study protocols, and statistical analysis files are available from the corresponding author upon reasonable request. Relevant materials will be retained and accessible for 5 years after official publication.

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.

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Disclosure

The authors have no competing interests to declare.

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