

The ED₅₀ of Remazolam Toluenesulfonate Combined with a Subthreshold Dose of Esketamine for Inhibiting Cardiovascular Response to Tracheal Intubation in Elderly Patients

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Abstract: *Objective:* To explore the half-effective dose (ED₅₀) of remazolam toluenesulfonate combined with subthreshold amounts of esketamine for inhibiting cardiovascular response to tracheal intubation in elderly patients. *Method:* We included 42 patients, aged 65–75, who required general anesthesia and single-lumen endotracheal intubation for elective surgery. The first patient was administered remazolam toluenesulfonate at a dose of 0.20 mg/kg. Once the patient lost consciousness, their alertness/sedation score (OAA/S score) was ≤ 1, and their BIS score was ≤ 60, and a subthreshold dose (0.3 mg/kg) of esketamine was given. The subsequent doses were adjusted using a sequential approach based on the cardiovascular response to tracheal intubation observed in the previous patient. The dose was modified in increments or decrements of 0.01 mg/kg. The ED₅₀ and 95% CI of remazolam toluenesulfonate were calculated using the Dixon and Massey sequential distribution test method. *Result:* The inhibition of endotracheal intubation response was positively correlated with the dose of remazolam toluenesulfonate, and the depth of sedation could not be achieved when the amount was ≤ 0.22 mg/kg. The ED₅₀ of remazolam toluenesulfonate combined with a subthreshold dose of esketamine in inhibiting cardiovascular response to tracheal intubation in elderly patients was 0.30 (0.28, 0.33) mg/kg. There was no statistically significant difference in blood pressure between the induction of anesthesia and before the operation. *Conclusion:* When compounded with 0.3 mg/kg esketamine, the ED₅₀ of Remazolam toluenesulfonate in inhibiting cardiovascular response to endotracheal intubation in elderly patients was 0.30 mg/kg (95 % CI 0.28–0.33 mg/kg).

Keywords: Remazolam toluenesulfonate; Subthreshold dose; Esketamine; Elderly; Endotracheal intubation; Dose-effect relationship; ED₅₀

Online publication: November 27, 2023

1. Introduction

The seventh national census in 2021 showed that the population over 60 years old in China has reached 267.42 million, accounting for 18.7 %, an increase of 5.44 percentage points compared to 2010^[1]. The organ functions of elderly patients are weaker than younger patients, so the incidence of comorbidities is higher. Moreover,

elderly patients are less tolerant to narcotic analgesic and sedative drugs compared to middle-aged and young patients [2,3].

A study by Ball *et al.* found that intraoperative hemodynamic events were more frequent than respiratory events during surgery compared to respiratory problems [4]. At the same time, multiple cohort studies have found that acute hypotension is significantly associated with adverse outcomes in the acute phase, such as all-cause mortality, acute kidney injury, myocardial injury, heart failure, acute stroke, cognitive decline, and postoperative delirium [5-8]. There is some kind of relationship between induced hypotension and postoperative hypotension [9]. Therefore, hemodynamic stabilization during anesthesia induction is crucial for the prognosis of elderly patients.

Remazolam toluenesulfonate is a new type of benzodiazepine that mainly acts on gamma-aminobutyric acid (GABA) receptors. It was approved for induction and maintenance of general anesthesia in November 2021. Preliminary studies have found that it has the characteristics of fast induction, fast recovery, and stable hemodynamics. Esketamine is an enantiomer of ketamine, which mainly acts on N-methyl-D-aspartate (NMDA) receptors to induce anesthesia and analgesia. It is a commonly used sedative and anesthetic drug in clinical practice, and it is usually administered together with benzodiazepines. At the same time, the vagal response in elderly patients is enhanced, resulting in more apparent changes in heart rate. In contrast, the low-frequency components (LF) and high-frequency components (HF) of remazolam toluenesulfonate and esketamine have opposite effects [10,11], which may be the theoretical basis for the combination of the two drugs.

Endotracheal intubation involves intense and brief stimulation, which can potentially lead to significant hemodynamic fluctuations and hypotension from anesthesia induction to the start of surgery, ultimately impacting patient outcomes. Given the lack of prior research on the combination of remazolam toluenesulfonate and esketamine, this study aims to investigate the effects of different subthreshold doses of esketamine in combination with remazolam tosylate.

2. Material and methods

2.1. General information

This study is a prospective, single-center investigation focused on establishing a dose-response relationship, along with the observation and follow-up of adverse events. This experiment was approved by the Ethical Review Committee of Dazhu County People's Hospital, and all subjects participated voluntarily and signed informed consent.

The research subjects of this experiment were surgical patients hospitalized in Dazhu County People's Hospital from March 1, 2022, to February 28, 2023, who needed general anesthesia with endotracheal intubation.

Inclusion criteria: (1) age 65–75 years old, (2) ASA I-II, (3) signed an informed consent.

Exclusion criteria: (1) allergic to benzodiazepines, esketamine, and any excipients; (2) presence of myasthenia gravis; (3) presence of schizophrenia; (4) presence of severe depression; (5) poorly controlled or untreated hypertensive patients (resting systolic/diastolic blood pressure > 180/100 mmHg); (6) untreated or undertreated hyperthyroid patients; (7) presence of hemorrhagic heart disease; (8) other conditions that were deemed unsuitable by our team.

2.2. Anesthesia methods

All patients fasted for 6 hours, and water-fasted for 2 hours. Their BP, HR, SpO₂, T, PetCO₂, BIS, and muscle relaxation were monitored before entering the operating room. Their peripheral/central veins were opened,

and no pre-anesthesia medication was given. Anesthesia induction started after 3 min 6L/min mask oxygen inhalation was carried out. According to a previous study ^[12], 0.2 mg/kg Remazolam toluenesulfonate was given to the first patient, and after the patient lost consciousness (the OAA/S ≤ 1 and BIS ≤ 60), 1.5 mg/kg intravenous lidocaine was given sequentially, along with 0.3 mg/kg esketamine, 0.7 mg/kg rocuronium bromide. The T1 maximum inhibition degree of TOF was monitored according to muscle relaxation. Lidocaine topical anesthesia was applied for 2 minutes, and endotracheal intubation was performed under a video laryngoscope.

2.3. Sequential method

Dosage adjustment was performed using Dixon's modified sequential method: the dose of the first patient was selected as 0.2 mg/kg, the amount of remazolam toluenesulfonate for the second patient was determined by the response of the first patient, and the adjacent interval dose was 0.01 mg/kg, that is, if the first case is positive, the second case will be increased by 0.01 mg/kg, if it is negative, the reaction will be reduced by 0.01 mg/kg, and so on ^[13].

According to previous studies ^[14], the criteria for determining a positive cardiovascular response were as follows: (1) HR or MAP fluctuated by $\geq 20\%$ compared to the baseline value within 3 minutes after intubation, or HR exceeded 120 bpm, or blood pressure exceeded 180/100 mmHg when the endotracheal tube was inserted; (2) an OAA/S score of > 1 point or a BIS value of > 60 within 3 minutes after the injection of remazolam toluenesulfonate were also considered positive. Additional administration of 2 mg of remazolam tosylate was given until the OAA/S score was ≤ 1 and BIS was ≤ 60 . The dose of remazolam toluenesulfonate for the next patient was increased by one dose step.

2.4. Sample size

According to the research of Chen et al. ^[15], the study was terminated when seven positive-negative crossover points were completed.

2.5. Observation indicators

The recorded physiological parameters included MAP, HR, and oxygen saturation (SpO₂) at five specific time points: before the induction of anesthesia (T1), when the initial BIS reached or was maintained at a level of 60 or below (T2), 1 minute after endotracheal intubation (T3), 5 minutes post-intubation (T4), and just before the commencement of surgery (T5). Throughout the monitoring, adverse events such as hypotension and bradycardia were documented to comprehensively assess cardiovascular and physiological responses to anesthesia induction and intubation.

2.6. Statistical analysis

Data analysis was conducted using SPSS 22.0 and R language. For dose data that conformed to a normal distribution, it was presented as mean \pm standard deviation. The ED₅₀ level with a 95% confidence interval (CI) for remazolam toluenesulfonate was calculated using the Dixon and Massey sequential distribution test method formula ^[16]. The specific procedure involved recording the number of effective cases (a) representing the negative intubation reaction group and the number of ineffective cases (b) representing the positive intubation reaction group for each incremental dosage of Remazolam toluenesulfonate. Additionally, it included calculating the logarithm of each dose (lgX) and the total number of effective and ineffective intubation cases at that dose (n), the effective rate (p), and the difference between the logarithms of two adjacent gradient doses (d). The logarithmic value of ED₅₀ (lg ED₅₀) was computed as $\Sigma clgX/\Sigma c$, and the antilogarithm of this value provided the ED₅₀. The 95% CI was determined as $lg^{-1}(lgED_{50} - 1.96SlgED_{50}, lgED_{50} + 1.96SlgED_{50})$.

3. Results

3.1. Cases included

Sequential trials were carried out in sequence according to the enrollment of patients. The trial was terminated after the 8th intersection point appeared after the 42nd patient completed the trial. The patients were numbered 1–42, and no patients dropped out halfway. The sample consisted of 15 males and 27 females, aged 70.7 ± 3.8 years and with an average BMI of $23.6 \pm 3.7 \text{ kg/m}^2$. The number and types of cases included 2 ASA I; 30 ASA II, and 10 ASA III. There was no significant difference between the effective and ineffective groups regarding gender, Markov grade, BMI, and ASA grade (**Table 1**).

Table 1. Comparison of general patient data

Feature	Effective	Ineffective	P
Male-to-female ratio	9/14	18/28	0.629
Markov classification			
II	14	28	1
Age (y)	70.6 ± 3.2	70.1 ± 2.9	0.402
BMI	23.1 ± 2.9	23.1 ± 3.2	0.978
ASA Rating			
I	1	1	0.344
II	9	21	
III	4	6	

3.2. Intubation response induced by different doses of remazolam toluenesulfonate under sequential test

The first three patients were given 0.20 mg/kg, 0.21 mg/kg, and 0.22 mg/kg remazolam toluenesulfonate, respectively. However, since their BIS values exceeded 60, they all achieved the desired level of sedation by receiving 2 mg of remazolam toluenesulfonate as a corrective measure. The remaining patients did not require additional remazolam toluenesulfonate intervention. The medication and the patients’ reaction towards remazolam toluenesulfonate are shown in **Figure 1**. The ED₅₀ of remazolam toluenesulfonate combined with subthreshold dose esketamine in inhibiting cardiovascular response to endotracheal intubation in elderly patients was 0.30 mg/kg and 95% CI (0.28, 0.33), as shown **Table 2**.

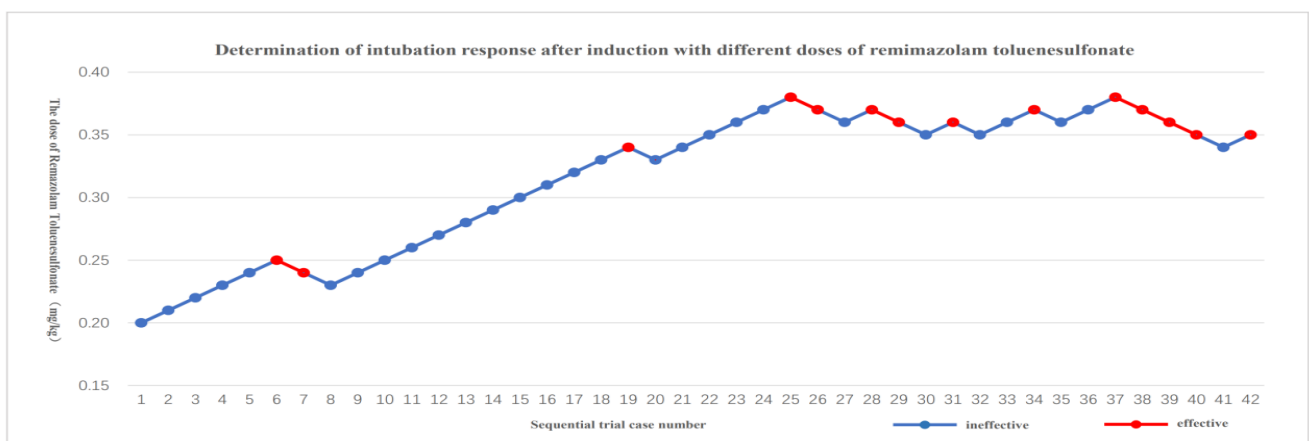


Figure 1. Determination of intubation response after induction with different doses of remazolam toluenesulfonate in a sequential trial

Table 2. Dixon and Massey's method was used to calculate the ED₅₀ and 95% CI of Remazolam toluenesulfonate (mg/kg)

Dose (X)	logX	Number of effective cases (a)	Number of ineffective cases (b)	Total number of cases (n)	nlogX	Efficiency (p)
0.20	-0.70	0	1	1	-0.70	0
0.23	-0.64	1	1	2	-1.28	0.5
0.25	-0.60	1	1	2	-1.20	0.5
0.33	-0.48	1	1	2	-0.96	0.5
0.34	-0.47	1	2	3	-1.41	0.33
0.35	-0.46	2	3	5	-2.3	0.4
0.36	-0.44	1	2	3	-1.32	0.33
0.37	-0.43	4	2	6	-2.58	0.33
0.38	-0.42	2	0	2	-0.84	1
Total	-4.64	13	13	26	-12.59	3.89

Note: The ED was calculated with the formula: $\lg ED_{50} = \frac{\sum n \lg X}{\sum n} = 0.48$, the antilog was used to obtain an ED₅₀ of 0.30; 95%CI = (0.28, 0.33)

3.3. MAP, HR, SpO₂ at each time point of patients and adverse reactions

There was no significant difference in the MAP of patients at T2, T4, and T5. Still, the MAP of patients at the T3 time point 1 min after intubation was significantly higher than before anesthesia induction. At T3 and T4, the heart rate of patients increased significantly compared to before induction of anesthesia, but there were no significant changes in the SpO₂ (Table 3).

One patient experienced coughing once after administration of remazolam toluenesulfonate, which resolved spontaneously in about 1 minute without decreased blood oxygen saturation and increased airway resistance. No patient had adverse reactions such as hypertensive crisis, severe hypotension, bradycardia, and decreased oxygen saturation. At the same time, in our trial, it was found that with the increase of the dose of remazolam toluenesulfonate, the time for the depth of sedation to reach OAA/S score ≤ 1 and BIS ≤ 60 was significantly shortened, but blood pressure did not decrease significantly.

Table 3. Comparison of MAP, HR, and SpO₂ at different time points

Index	Before anesthesia induction (T ₁)	Initial BIS ≤ 60 (T ₂)	1 min after intubation (T ₃)	5 min after intubation (T ₄)	Before surgery (T ₅)
MAP (mm Hg)	79.6 \pm 9.8	76.9 \pm 7.6	89.7 \pm 9.6 ^a	80.5 \pm 9.2	78.9 \pm 8.3
HR (times/min)	72.3 \pm 6.7	69.9 \pm 6.5	87.6 \pm 10.1 ^a	83.6 \pm 9.3 ^a	76.8 \pm 7.2
SpO ₂ (%)	98.5 \pm 1.8	99.4 \pm 0.5	99.5 \pm 0.5	99.7 \pm 0.3	99.6 \pm 0.4

Compared with T1, ^aP < 0.05

4. Discussion

Endotracheal intubation stimulates the respiratory tract mechanically, and then causes excited hypothalamus-sympathetic-adrenal medulla system, thereby increasing the concentration of catecholamines, HR, and BP. Fluctuating main noxious stimuli can easily lead to an imbalance of blood supply to essential organs and even cardiac arrest^[17]. The results of this study showed that the ED₅₀ of primary remimazolam sulfonate compound subthreshold dose (0.3 mg/kg) esketamine for inhibiting cardiovascular response to endotracheal intubation in elderly patients was 0.30 (0.28, 0.33) mg/kg. In line with a prior investigation^[18], the dose of remazolam

tosylate and the duration required to attain a BIS value of 60 or lower are correlated with dosage; however, this may be accompanied by a reduction in blood pressure and heart rate. In this study, the combined administration of remazolam toluenesulfonate and a subthreshold dose of esketamine for anesthesia induction, from the initiation of anesthesia induction until the start of the surgery, was found to result in more stable hemodynamic conditions in elderly patients.

This study used a sequential experimental method to explore the ED₅₀ and 95%CI of Remazolam toluenesulfonate combined with subthreshold dose esketamine in inhibiting cardiovascular response to endotracheal intubation in elderly patients. This method is efficient in determining the half-effective dose. A total of 42 patients were included in this test, and there were seven intersection points from positive reaction to adverse reaction, which was close to the number of ED₉₀ cases in similar studies^[19], which also explained the reliability of the sample size and the stability of the results to a certain extent.

The dose of remazolam toluenesulfonate selected for the first elderly patient in this study was 0.2 mg/kg^[12]. The dosage was increased for the subsequent patients. Considering that it may be related to the pharmacological mechanism of the two drugs^[20,21], it may be that remazolam toluenesulfonate has little influence on hemodynamics and even at subthreshold doses, esketamine exerts a stimulating effect on circulation. This partially explains the relative hemodynamic stability observed when both drugs were used together for endotracheal intubation in elderly patients from the induction of anesthesia to the start of surgery.

This study has several limitations: (1) It is the first investigation into the combination of remazolam toluenesulfonate and esketamine. Due to safety considerations, the study was restricted to individuals aged 65–75 years, limiting the generalizability of the findings. (2) There are notable variations in the responsiveness of elderly patients, including differences in frailty and underlying health conditions. These confounding variables could impact the results. However, the study's inclusion of a similar number of cases to that of ED₉₀ cases enhances the reliability of the findings to a certain extent.

5. Conclusion

When compounded with 0.3 mg/kg esketamine, the ED₅₀ of remazolam toluenesulfonate in inhibiting cardiovascular response to endotracheal intubation in elderly patients was 0.30 mg/kg (95 % CI 0.28-0.33 mg/kg). The combination of the two may effectively reduce the incidence of hypotension after anesthesia-induced intubation and before surgery. Still, the sample size of this study is small, and further multi-center, large-sample randomized controlled studies are needed.

Disclosure statement

The author declares no conflict of interest.

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