# Exploring the $ED_{50}$ and $ED_{95}$ of Remimazolam for Laryngeal Mask Airway Insertion During General Anesthesia in Pediatric Strabismus Correction Surgery

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AIM: Remimazolam, known for its rapid onset, quick metabolism, and short recovery time from sedation, offers significant advantages in clinical anesthesia. Previous studies have primarily investigated its application in adult surgical anesthesia, with less focus on its utilization in pediatric patients. Therefore, we aimed to explore the 50% effective dose ($ED_{50}$) and 95% effective dose ($ED_{95}$) of remimazolam for laryngeal mask airway (LMA) insertion during general anesthesia in pediatric strabismus correction surgery and investigate its dose-response relationship, thereby providing valuable reference data for safer and more rational clinical use of remimazolam.

METHODS: This study included 32 patients aged 3–12 years undergoing strabismus correction surgery at Ningbo Aier Guangming Eye Hospital in 2024. The dosage of remimazolam was determined according to the Dixon 'up-and-down' sequential method: the starting induction dose was 0.2 mg/kg, with a step dose of 0.05 mg/kg. In cases of positive anesthetic effect, the subsequent patient received a reduced step dose, while in cases of negative anesthetic effect, the next subject received an increased step dose. The trial was terminated upon observing seven "positive-negative" crossover points. Furthermore, the $ED_{50}$ and $ED_{95}$, along with their 95% confidence intervals (95% CI) were calculated using the Probit regression analysis. Additionally, vital signs of the patients, such as peripheral oxygen ($SpO_2$), heart rate, and blood pressure, along with the incidence of adverse events, were monitored.

RESULTS: The $ED_{50}$ of remimazolam for LMA insertion in pediatric strabismus correction surgery was 0.300 mg/kg (95% CI 0.276–0.323 mg/kg), and the $ED_{95}$ was 0.369 mg/kg (95% CI 0.324–0.414 mg/kg). Throughout the surgery, $SpO_2$, heart rate, and blood pressure remained stable without any significant fluctuations.

CONCLUSIONS: The $ED_{50}$ and $ED_{95}$ of remimazolam for LMA insertion in pediatric strabismus correction surgery are 0.300 mg/kg and 0.369 mg/kg, respectively. This study demonstrates that remimazolam is both safe and effective for LMA insertion during general anesthesia in pediatric strabismus correction surgery.

**Keywords:** remimazolam; pediatric strabismus correction surgery; laryngeal mask airway; up-and-down sequential method; 50% effective dose ($ED_{50}$)

## Introduction

The ideal characteristics of an anesthetic induction sedative include rapid onset, quick recovery from sedation, and minimal adverse reactions, such as hypotension and circulatory depression [1, 2]. Remimazolam, a novel ultra-short-acting benzodiazepine, offers significant advantages in clinical anesthesia due to its rapid onset, fast metabolism, and quick recovery from sedation. It was approved by the US Food and Drug Administration (FDA) in July 2020, the European Medicines Agency (EMA) in March 2021, and China in December 2021 [3].

Currently, midazolam is the most commonly used benzodiazepine [3]. However, its metabolism by cytochrome P450 enzymes (CYP3A) poses limitations due to potential drug interactions during sedation applications [4]. Conversely, remimazolam distinguished from traditional midazolam in that its inactive metabolites are quickly metabolized by tissue esterases into inactive compounds and predominantly excreted by the kidneys. This helps to reduce potential residual effects and the risk of cumulative toxicity [5]. Remimazolam maintains stable hemodynamic characteristics during and after anesthesia induction, making it particularly suitable for medical situations requiring rapid recovery of consciousness, such as day surgeries, endoscopic procedures (like colonoscopy and bronchoscopy), and the induction and maintenance of general anesthesia [3].

Besides its high safety profile, remimazolam induction is known for its minimal injection pain [6]. Moreover, its sedative effects can be easily managed, with rapid reversal achieved by administering flumazenil, a specific benzodiazepine antagonist, allowing patients to awaken quickly [7, 8]. This feature is crucial for ensuring patient safety and enhancing medical efficiency.

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As a new drug, the use of remimazolam in general anesthesia still requires extensive dose-related data to address various clinical needs. Previous studies have investigated the effective induction doses of remimazolam in various types of surgeries involving adult subjects. In a study by Chen *et al*. [9], remimazolam was administered to elderly patients undergoing gastric examinations, revealing remimazolam as effective as propofol in achieving anesthetic outcomes but with a lower incidence of adverse events. Similarly, Fan *et al*. [10] reported that remimazolam applied during hysteroscopy was a safer and more effective anesthesia option than propofol.

Although remimazolam has been extensively studied for anesthesia-related applications in adults, its efficacy in pediatric population remains underexplored. A meta-analysis of 18 studies (mostly case reports) indicated that remimazolam is a safe and effective option in children [11]. In a clinical study involving 418 children with a mean age of 4.6 years, remimazolam was used as a general endotracheal anesthetic at 12 mg/kg/h for induction and 1–2 mg/kg/h for maintenance. The results revealed that remimazolam offers the advantages of rapid postoperative recovery in pediatric anesthesia. However, there is a risk of hemodynamic variability, potentially related to the dosage of injection [12]. Generally, the lack of specific pediatric dosing guidelines poses certain challenges. Given its advantages, such as no injection pain, rapid onset, short half-life, predictable sedation levels, quick recovery from anesthesia, relatively stable respiratory and circulatory function, and the availability of a specific antagonist, remimazolam appears to be particularly well-suited for pediatric use [13].

Strabismus correction surgery is a common ophthalmic procedure in children [12]. Traditional anesthesia methods for pediatric ophthalmic surgeries, such as endotracheal intubation or intravenous anesthesia pose the risk of airway irritation and respiratory depression, potentially affecting the child's safety. The laryngeal mask airway (LMA), a novel ventilation device, offers advantages such as ease of use and minimal airway irritation, making it a viable alternative to tracheal intubation in many situations [14, 15]. A well-planned and comprehensive anesthesia protocol is critical for the successful and safe execution of pediatric ophthalmic procedures. Therefore, our study aims to assess the 50% effective dose ($ED_{50}$) of remimazolam for LMA insertion, utilizing dosing guidelines established for adults, focusing on pediatric patients undergoing general anesthesia for strabismus correction surgery, and to evaluate its safety.

## Materials and Methods

*Recruitment of the Study Participants*

The study recruited 32 children aged 3–12 years who underwent ophthalmic surgery at Ningbo Aier Guangming Eye Hospital in 2024. This study was approved by the Medical Ethics Committee of Ningbo Aier Guangming Eye Hospital (SL-AIER-KY-2024-08), and written informed consent was obtained from all participants.

Inclusion criteria of study participants were as follows: individuals with age between 3–12 years, body mass index (BMI) of 14–25 kg/m$^2$, American Society of Anesthesiologists (ASA) physical status classification of I or II, scheduled for general anesthesia for ophthalmic strabismus correction surgery and suitable for LMA insertion.

However, exclusion criteria of study participants included a history of neuropsychiatric disorders, anticipated difficult airway or difficult mask ventilation, having planned anesthesia methods other than general anesthesia, those with chronic obstructive pulmonary disease, asthma, pneumonia, or active upper respiratory tract infection, known use of drugs that interact with benzodiazepines, such as sedatives, proton pump inhibitors, or certain antibiotics and those who are allergic to benzodiazepines or opioid medications.

Furthermore, this study set rule-out criteria for study participants and excluded those who did not meet the inclusion criteria or whose guardians requested to withdraw from the study. Similarly, patients with incomplete clinical data or missing crucial clinical parameters were also excluded from the study cohort.

*Study Design*

This study used various drugs. Remimazolam tosilate injection (NMPA approval number: H20190034, Lianyungang, China) was obtained from Jiangsu Hengrui Pharmaceuticals Co., Ltd., and Remifentanil Hydrochloride injection (NMPA approval number: H20143314, Xuzhou, China) was procured from Jiangsu Nhwa Pharmaceutical Co., Ltd. Moreover, Rocuronium bromide injection (NMPA approval number: H20183109, Qingyuan, China) was provided by Guangdong Jiabo Pharmaceutical Co., Ltd., and Atropine Sulfate injection (NMPA approval number: H32021535, Chengdu, China) was purchased from Chengdu Brilliant Pharmaceutical Co., Ltd.

Upon arrival in the operating room, an intravenous line was established for each patient, and standard monitors (IM20, EDAN, Shenzhen, China) were used to assess non-invasive blood pressure, electrocardiogram, and pulse oximetry. Before induction, atropine (0.01 mg/kg) was administered intravenously, and patients were pre-oxygenated with 100% oxygen under spontaneous breathing conditions.

An anesthesiologist administered the induction drugs intravenously, delivering 0.2 mg/kg of remimazolam and 2 μg/kg of remifentanil over a period of 2 minutes. The exact time of remimazolam administration completion was recorded. After 150 seconds, another anesthesiologist, blinded to the remimazolam dose, assessed and recorded the patient's level of loss of consciousness (LOC) using the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score [16]. The MOAA/S score is a tool used to assess the level of consciousness or sedation depth in pa-

tients under anesthesia or sedative medications. A patient with a score 5 responds readily to a name spoken in a normal tone, 4 shows a lethargic response to a name spoken in a normal tone, 3 responds only after the name is called loudly or repeatedly, 2 responds only after mild prodding or shaking, 1 responds only after painful trapezius squeeze, and 0 does not respond even after painful trapezius squeeze.

Before LMA insertion, certain conditions were ensured in patients, such as successful LOC (defined as MOAA/S $<2$), cessation of spontaneous breathing, and 150 seconds post-remimazolam injection. Once these criteria were satisfied, the anesthesiologist who assessed the LOC inserted the LMA. The outcomes were classified into successful (Positive group) or unsuccessful (Negative group). The successful (positive) anesthesia was defined by the smooth insertion of the LMA, observation of symmetrical chest wall movement under mechanical ventilation, and a normal rectangular end-tidal $CO_2$ ($EtCO_2$) waveform. Smooth insertion criteria included no involuntary movements, no resistance when opening the patient's mouth, and no coughing or laryngospasm. However, the failed (negative) anesthesia was determined as the patient experiencing significant throat pain or coughing during LMA insertion, leading to the unsuccessful placement of the laryngeal mask.

The remimazolam induction dose for each patient was determined using Dixon 'up-and-Down' sequential method [17, 18]. Based on previous studies and our clinical experience, the initial dose of remimazolam was set at 0.2 mg/kg with a dose interval of 0.05 mg/kg. Consequently, the first patient received 0.2 mg/kg of remimazolam. In the case of successful LMA insertion, the subsequent patient's dose was reduced by 0.05 mg/kg. Conversely, if the insertion failed, the next patient's remimazolam induction dose was increased by 0.05 mg/kg, following this pattern. The study was terminated when the "positive response" and "negative response" alternated seven times (i.e., there were seven crossovers).

To ensure patient safety and comfort, the procedure was attempted only once. In unsuccessful cases, the patient immediately received 10–20 mg of rocuronium bromide intravenously, and anesthesia was maintained by infusing 1–2 mg/kg/h of remimazolam and 0.1–0.3 μg/kg/min of remifentanil. However, in successful cases, anesthesia during surgery was maintained by infusing 1–2 mg/kg/h of remimazolam and 0.1–0.3 μg/kg/min of remifentanil.

*Observational Indicators*

Vital signs of the patients were recorded at the following time points: pre-anesthesia baseline (T0), at loss of consciousness (LOC, T1), immediately after LMA insertion (T2), 1 minute after LMA insertion (T3), 3 minutes after LMA insertion (T4), and 5 minutes after LMA insertion (T5). During the study period, if the patient's systolic blood pressure (SBP) dropped more than 20% below baseline, dopamine was administered intravenously. If the heart rate (HR) fell below 50 bpm, atropine was administered intravenously.

*Observation of Adverse Events*

During LMA insertion, the following adverse events were closely monitored: occurrences of air leakage or other movements, respiratory complications (including laryngospasm, bronchospasm, reflux, or aspiration), circulatory depression, postoperative agitation, postoperative nausea, vomiting, and pain.

*Statistical Analysis*

Data were statistically analyzed using SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was assessed utilizing the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean $\pm$ standard deviation (SD). Furthermore, changes in the data over different time points were analyzed using one-way ANOVA followed by post hoc analysis with Dunnett's multiple comparisons test. However, comparisons between the two groups were performed using the *t*-test, and enumeration data were analyzed using the Chi-square ($\chi^2$) test. A $p$-value $< 0.05$ was considered statistically significant. Probit regression analysis was used to determine the 50% effective dose ($ED_{50}$) and 95% effective dose ($ED_{95}$) of the population, along with their respective 95% confidence intervals (CI). The dose-response curve and sequential graph for remimazolam were generated using GraphPad Prism version 8.0 (GraphPad Software LLC, San Diego, CA, USA).

## Results

*Patient Information*

This study enrolled 32 patients, including 13 males and 19 females. The study participants were classified as ASA Physical Status I and cooperated throughout the study procedure. The average age of the patients was $8.4 \pm 2.6$ years, average weight was $36.5 \pm 10.9$ kg, average height was $141.7 \pm 17.0$ cm, and average body mass index (BMI) was $17.7 \pm 2.5$. The flow chart of the study design and patient's characteristics are shown in Fig. 1 and Table 1, respectively.

*Dose-Response*

The sequential dose adjustment of remimazolam is shown in Fig. 2. Out of the 32 patients, 19 successfully underwent LMA insertion (positive) after a single injection of remimazolam, while 13 did not achieve successful insertion (negative). Patients with unsuccessful sedation received an additional dose of rocuronium. Using the success rates of LMA insertion across different dosage groups, a dose-response curve of remimazolam in LMA insertion during pediatric strabismus correction surgery was constructed (Fig. 3).

The Probit regression analysis yielded the following probability regression equation for remimazolam: Probit ($P$) =

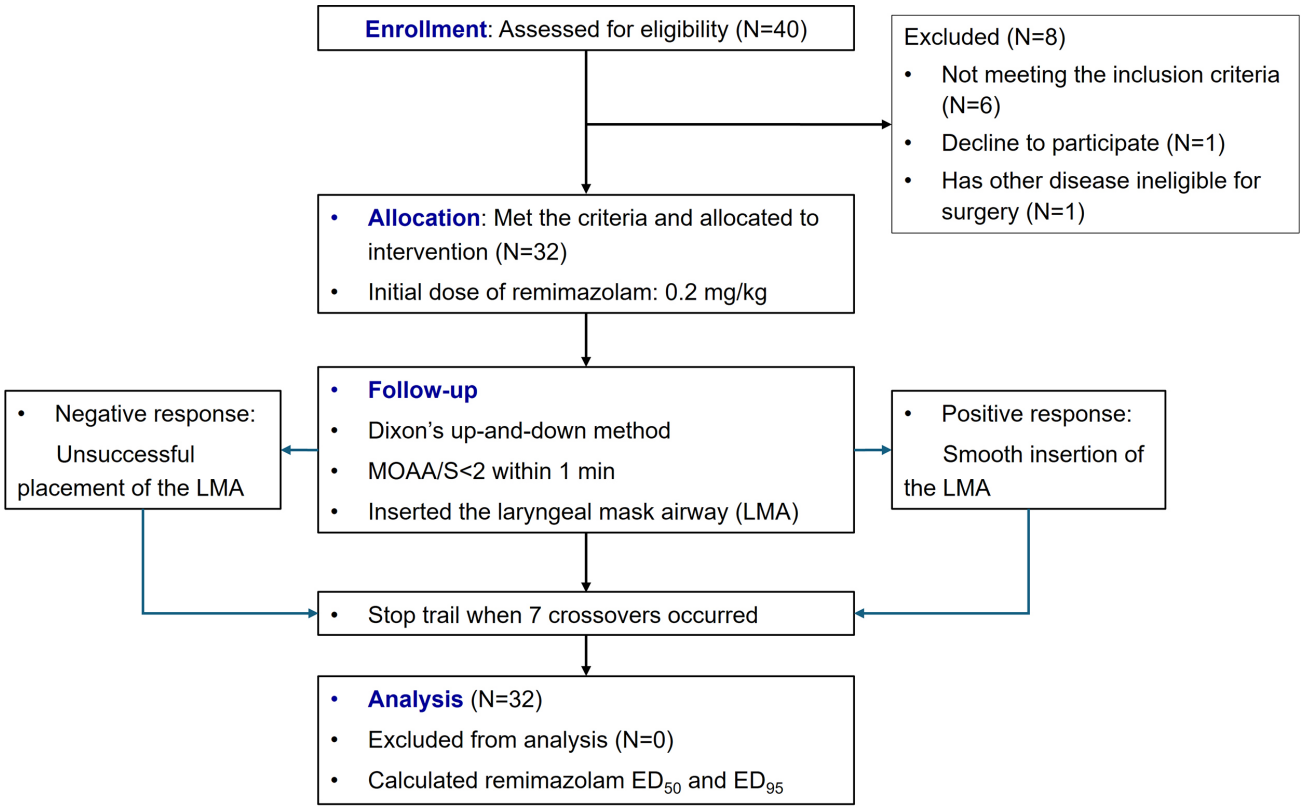


**Fig. 1. Flowchart of the study design based on Dixon 'up-and-down' method.** MOAA/S, Modified Observer's Assessment of Alertness and Sedation; $ED_{50}$, 50% effective dose; $ED_{95}$, 95% effective dose.

–7.12 – 23.769 × Dose. The fit of this equation was tested and found to be excellent, with a *p*-value of 0.861. The regression equation demonstrated that the $ED_{50}$ of remimazolam was 0.300 mg/kg (95% CI 0.276–0.323 mg/kg), while the 95% effective dose ($ED_{95}$) value was found to be 0.369 mg/kg (95% CI 0.324–0.414 mg/kg).

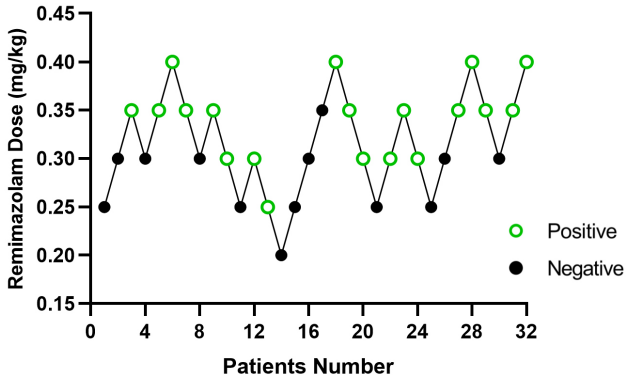


**Fig. 2. Sequential dose adjustment for remimazolam during the laryngeal mask airway (LMA) insertion under general anesthesia for pediatric strabismus correction surgery.** The initial dose of remimazolam was 0.2 mg/kg, and each subsequent dose was increased or decreased by 0.05 mg/kg.

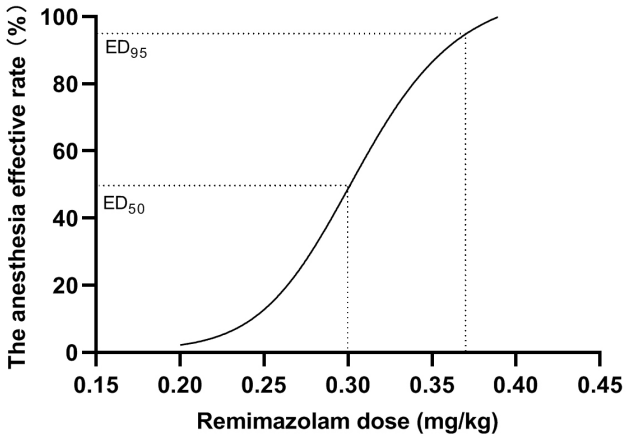


**Fig. 3. Dose-response curve for remimazolam during LMA insertion under general anesthesia for pediatric strabismus correction surgery, generated using Probit regression analysis.**

*Changes in the Vital Signs and Clinical Indicators of the Patients*

We observed that the saturation of peripheral oxygen ($SpO_2$) elevated significantly after remimazolam administration. The heart rate (HR) remained relatively stable from T1 to T5 compared to the baseline values at T0, indicating minimal fluctuation. However, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased

**Table 1. Baseline characteristics of the study participants.**

| | Patients (N = 32) | Positive (N = 19) | Negative (N = 13) | $t/\chi^2$ | *p*-value |
|---|---|---|---|---|---|
| Sex (Male/Female) | 13/19 | 8/11 | 5/8 | 0.042[a] | 0.837 |
| Age (Year) | 8.4 ± 2.6 | 8.6 ± 2.6 | 8.0 ± 2.6 | 0.641 | 0.526 |
| Weight (kg) | 36.5 ± 10.9 | 39.0 ± 11.2 | 32.8 ± 9.6 | 1.627 | 0.114 |
| Height (cm) | 141.7 ± 17.0 | 144.5 ± 15.8 | 137.6 ± 18.5 | 1.132 | 0.267 |
| BMI ($kg/m^2$) | 17.7 ± 2.5 | 18.1 ± 2.9 | 17.2 ± 1.5 | 1.025 | 0.313 |
| ASA physical status classification | | | | | |
| ASA-I | 32 | 19 | 13 | / | / |

Note: [a]Chi-square ($\chi^2$) analysis was used to assess the gender differences between groups. BMI, body mass index; ASA, American Society of Anesthesiologists.

following the administration of remimazolam, but the reductions remained within a safe range of less than 20% (Fig. 4). These findings demonstrate that remimazolam maintains stable hemodynamic characteristics.

*Adverse Events*

Among all patients, 2 individuals (6.3%) experienced nausea, and neither of the patients experienced vomiting. Furthermore, 1 (3.1%) patient exhibited agitation (Table 2). These adverse events resolved spontaneously without intervention. There were no other adverse reactions among the remaining patients.

**Table 2. The occurrence of adverse reactions among the study participants.**

| Adverse reactions | Patients |
|---|---|
| Hypoxaemia | 0/32 |
| Bradycardia | 0/32 |
| Nausea | 2/32 |
| Vomiting | 0/32 |
| Choking and coughing | 0/32 |
| Dysphoria | 1/32 |

## Discussion

Pediatric strabismus correction surgery presents a unique category of surgical procedures, involving young patients. The LMA has become a popular choice for airway management during these surgeries due to its ease of use, minimal airway irritation, and straightforward placement and removal [14, 19]. The surgical procedure is typically conducted under general anesthesia, necessitating high precision in administering anesthetic, primarily because the ease of LMA insertion impacts the success of the surgery and the comfort of the patient.

Remimazolam, known for its rapid onset, quick recovery, and minimal impact on the cardiovascular system, has been extensively used in endoscopic procedures (such as gastroscopy, colonoscopy, and other endoscopic surgeries), day surgeries, and surgeries involving elderly patients [20]. Compared to midazolam and propofol, remimazolam offers an enhanced safety profile because its effects are quickly reversed by flumazenil, a specific antagonist, which is not available for propofol [21]. Studies indicate that remimazolam provides better safety than propofol when used for anesthesia during gastroscopy or colonoscopy [9, 22].

The Dixon 'up-and-down' sequential method is widely utilized in current clinical drug research [23]. This method is a classical and cost-effective approach for determining the effective concentration of a drug. It does not require a predetermined sample size; each experiment is analyzed promptly, and the study can be terminated as soon as a conclusion is reached. Its advantages include the need for fewer study subjects (typically a few dozen patients) and the ability to easily and rapidly calculate the drug's median effective dose. However, it is worth noting that in case of significant patient variability, a single Up-and-Down design may not adequately reflect the overall response, thus necessitating repeated or grouped analyses [23]. Xiao and colleagues [24] enrolled 27 patients and employed the 'up-and-down' sequential method to assess the anesthetic induction $ED_{50}$ and $ED_{95}$ of remimazolam in patients with sleep disorders undergoing laparoscopic cholecystectomy. The study demonstrated that the $ED_{50}$ of remimazolam was 0.226 mg/kg, and the $ED_{95}$ was 0.237 mg/kg [24]. Furthermore, in another study, the effective doses of remimazolam and propofol for anesthesia were investigated during gastroscopy examination in elderly patients, involving 23 and 20 patients, respectively. The results showed that the $ED_{50}$ of remimazolam was 0.153 mg/kg, while the $ED_{50}$ of propofol was 0.945 mg/kg [9]. Additionally, Qu and colleagues [25] investigated the $ED_{95}$ of remimazolam for suppressing tracheal intubation-related cardiovascular responses in frail and non-frail elderly patients during anesthesia induction. The findings revealed that in frail and non-frail elderly patients, the $ED_{95}$ of remimazolam was 0.297 mg/kg and 0.331 mg/kg, respectively [25].

Therefore, the effective dosage of remimazolam may vary among different patient demographics and surgery types. However, to our knowledge, there have been no published reports on using remimazolam for LMA insertion during

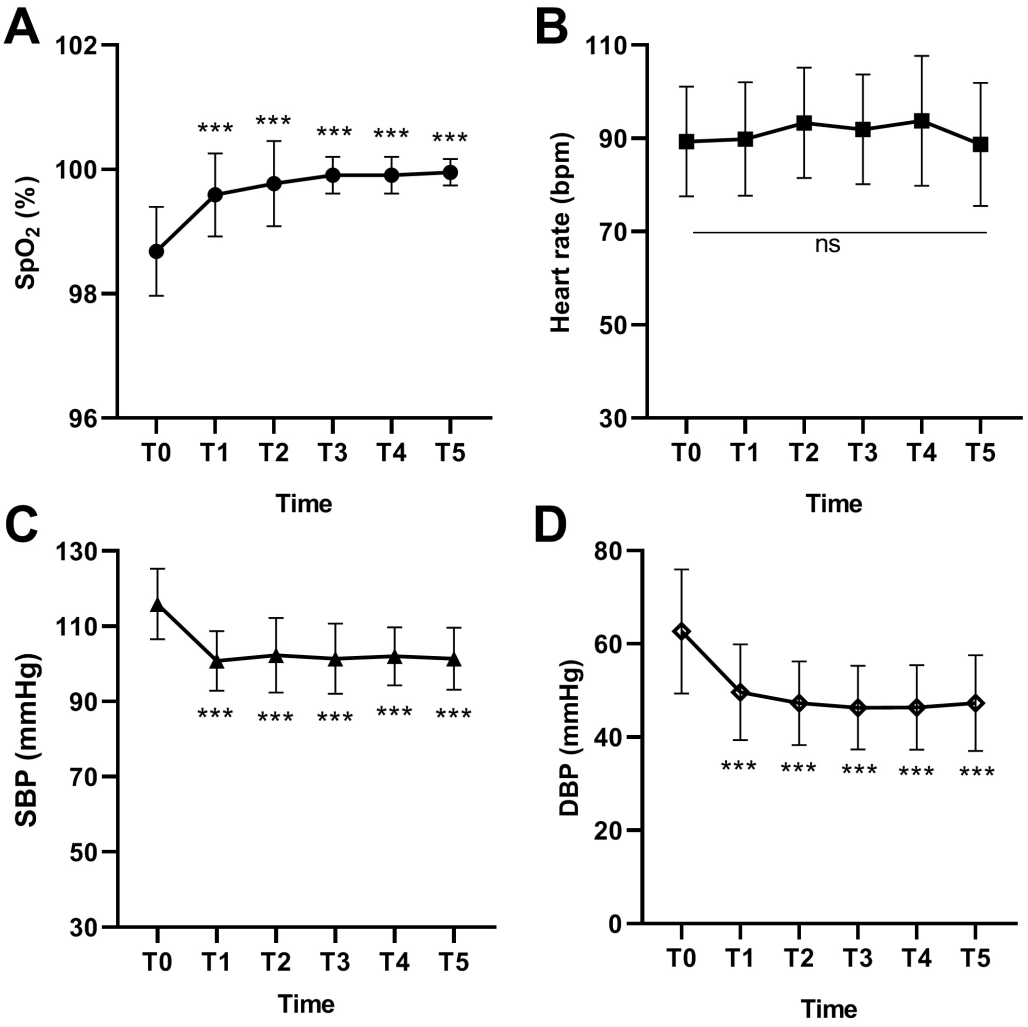


**Fig. 4. Changes in vital signs during the anesthesia induction process.** Comparison of changes in vital signs, including saturation of peripheral oxygen ($SpO_2$) (A), heart rate (B), systolic blood pressure (SBP) (C) and diastolic blood pressure (DBP) (D). Vital signs at pre-anesthesia baseline (T0), at the loss of consciousness (LOC) (T1), immediately after LMA insertion (T2), 1 minute after LMA insertion (T3), 3 minutes after LMA insertion (T4), and 5 minutes after LMA insertion (T5). Data are presented as mean ± standard deviation (SD). $^{***}p < 0.001$ for T1–T5 vs. T0; ns represents 'no significant difference'.

general anesthesia in children. This study explored the clinical efficacy and safety of remimazolam for LMA insertion in pediatric strabismus correction surgeries.

We observed that using remimazolam as a sedative before pediatric strabismus correction surgery effectively improved the success of LMA insertion. By exploring various dosages of remimazolam, we established that the $ED_{50}$ for LMA insertion during general anesthesia in pediatric strabismus correction surgery was 0.300 mg/kg (95% CI 0.276–0.323 mg/kg), and the $ED_{95}$ was 0.369 mg/kg (95% CI 0.324–0.414 mg/kg). The $ED_{50}$ value of remimazolam for general anesthesia in pediatric strabismus surgery is slightly higher than the corresponding value in adults, approximately 0.1–0.2 mg/kg. To date, only a few studies have described the pharmacokinetics of remimazolam in children. Two studies on the pharmacokinetic properties of remimazolam have revealed that its terminal half-life is similar in children and adults. In a pharmacokinetic study of remimazolam involving children aged 2–6 years, the terminal half-life of remimazolam was 67 minutes and the context-sensitive half-time was 17 minutes [26]. In contrast, in a study conducted in adults (aged 20–38 years), the terminal half-life of remimazolam was 70 minutes and the context-sensitive half-time was 6.8 minutes [27], suggesting a shorter duration compared to the data observed in children. Our study indicates a higher $ED_{50}$ value in pediatric anesthesia, which may be related to the type of surgery and the varying sensitivity of children to remimazolam. Additionally, the children in our study were aged 3–12 years, differing from the 2–6 years age range in the aforementioned study. Considering the difference in metabolic rates, blood volume, and cardiac responsiveness between children and adults, dose adjustments are necessary for pediatric applications [11].

Furthermore, our study revealed that after the administration of remimazolam, the $SpO_2$ and HR remained stable without significant fluctuations. This study specifically evaluated the hemodynamic stability induced by remimazolam anesthesia. It is known that hypotension can occur during and after anesthesia induction, posing a risk to patient safety. Hence, anesthesiologists aim to minimize hemodynamic fluctuations during and after anesthesia induction. Previous research has reported that compared to propofol, remimazolam is associated with less frequent cardiovascular depression during general anesthesia in adults [28]. In a study comparing propofol and remimazolam for sedation induction and maintenance in adults, the reduction in blood pressure was 20.0% and 24.0% in the 6 mg/kg/h and 12 mg/kg/h remimazolam groups, respectively, compared to 49.3% in the propofol group [29]. In a randomized controlled clinical trial, patients who received remimazolam at an induction dose of 0.2 mg/kg and a maintenance dose of 1.0 mg/kg/h had significantly lower rates of hypotension than those who were administered propofol at a dosage of 1.5 to 2.0 mg/kg [10]. Shi *et al*. [30] indicated a lower incidence of intraoperative hypotension and postoperative low $SpO_2$ in the remimazolam group compared to the propofol group. Our study demonstrated that although there was a slight decrease in SBP and DBP from T0 to T1–T5, all changes were below 20%. These findings suggest that remimazolam did not lead to significant cardiovascular depression, thereby maintaining good hemodynamic stability during the surgery.

Adverse events were closely monitored during the surgery. It was found that only two patients (6.3%) experienced nausea, with neither of them vomiting. Additionally, one patient (3.1%) exhibited agitation, but no other adverse reactions were observed among the remaining patients. All children could recover quickly and smoothly to a state of wakefulness after the surgery without any significant complications. Given that the surgery was for strabismus correction, the occurrence of postoperative nausea might also be related to the surgical procedure and not necessarily to the medication. In a study using propofol for general anesthesia during pediatric strabismus surgery, 17% of patients in the propofol group experienced postoperative nausea [31]. Conversely, in clinical studies of remimazolam for pediatric anesthesia, there have been minimal reports of side effects such as nausea, vomiting, or hypotension [11]. In a study of children undergoing elective adenotonsillectomy using midazolam as a general anesthetic, postoperative nausea and vomiting were observed in 15.6% and 11.1% of patients, respectively; however, 11.1% of patients experienced agitation [32]. Thus, overall, the safety profile of remimazolam for pediatric general anesthesia surpasses that of propofol and midazolam. These results suggest that using remimazolam for general anesthesia and LMA insertion in pediatric strabismus correction surgery is safe and effective.

However, since remimazolam is a relatively new drug in pediatric anesthesia and there is still an ongoing accumulation of experience with its use in this field, future studies involving larger scales and multiple centers are required to further validate its advantages in pediatric surgeries. It is also necessary to thoroughly explore the potential risks and side effects associated with its use, aiming to ensure the safety of children while fully leveraging the potential of remimazolam in pediatric anesthesia. Additionally, integrating remimazolam with other anesthetic agents to develop the most optimal anesthesia protocol will be crucial to enhance the perioperative experience of pediatric patients.

This study also has some limitations. Due to physiological differences between children and adults, including faster metabolism and significant changes in the body weight ratio to body surface area, adjusting the dose of remimazolam in children is complex and requires precise calculation and personalized administration. Incorrect dosing may lead to excessively deep or insufficient sedation, impacting surgical procedures and child safety. Furthermore, the age range of the children in our study was broad (3–12 years), and future studies could narrow this range to achieve more precise dosing. Additionally, all patients in this study were classified as ASA I. The applicability of remimazolam in pediatric patients classified as ASA II undergoing LMA insertion during strabismus correction surgery needs further evaluation in future studies. Furthermore, all children in the study underwent general anesthesia for strabismus correction, representing a single type of surgery. Therefore, additional studies are needed in other pediatric patient groups to validate the safety and efficacy of remimazolam in pediatric general anesthesia.

## Conclusions

This study investigated the $ED_{50}$ and $ED_{95}$ of remimazolam for LMA insertion during pediatric strabismus correction surgeries under general anesthesia. The study indicated that the $ED_{50}$ of remimazolam was 0.300 mg/kg (95% CI 0.276–0.323 mg/kg), and the $ED_{95}$ was 0.369 mg/kg (95% CI 0.324–0.414 mg/kg). Following the administration of remimazolam, we observed that $SpO_2$, HR, and blood pressure were maintained at stable levels without significant fluctuations. These observations suggest that remimazolam does not lead to substantial cardiovascular depression and maintains good hemodynamic stability during the surgery. These findings demonstrate that remimazolam is safe and effective for LMA insertion under general anesthesia in pediatric strabismus correction surgeries.

## Availability of Data and Materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

All authors contributed to this paper. QS, QL, BL, RCW, JLQ: investigation, data collection and analysis; QS: writing-original draft; WG, JLQ: formal analysis, visualization; JLQ: conceptualization, supervision, writing-reviewing; QS, QL: methodology. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

The present study followed the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of Ningbo Aier Guangming Eye Hospital (SL-AIER-KY-2024-08) and written informed consent was obtained from all subjects participating in the trial, and their information was stored and used for research anonymously.

## Acknowledgment

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

## References

[1] Tobias JD, Leder M. Procedural sedation: A review of sedative agents, monitoring, and management of complications. Saudi Journal of Anaesthesia. 2011; 5: 395–410.

[2] Eger EI, 2nd. Characteristics of anesthetic agents used for induction and maintenance of general anesthesia. American Journal of Health-system Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists. 2004; 61: S3–S10.

[3] Kim KM. Remimazolam: pharmacological characteristics and clinical applications in anesthesiology. Anesthesia and Pain Medicine. 2022; 17: 1–11.

[4] Peter JU, Dieudonné P, Zolk O. Pharmacokinetics, Pharmacodynamics, and Side Effects of Midazolam: A Review and Case Example. Pharmaceuticals (Basel, Switzerland). 2024; 17: 473.

[5] Kilpatrick GJ. Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent. Frontiers in Pharmacology. 2021; 12: 690875.

[6] Noor N, Legendre R, Cloutet A, Chitneni A, Varrassi G, Kaye AD. A comprehensive review of remimazolam for sedation. Health Psychology Research. 2021; 9: 24514.

[7] Worthington MT, Antonik LJ, Goldwater DR, Lees JP, Wilhelm-Ogunbiyi K, Borkett KM, *et al*. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. Anesthesia and Analgesia. 2013; 117: 1093–1100.

[8] Choi HR, Song IA. Review of remimazolam and sedatives in the intensive care unit. Acute and Critical Care. 2022; 37: 151–158.

[9] Chen D, Liao M, Wu XR, Zhao TYM, Sun H. Comparison of efficacy and safety of equivalent doses of remimazolam versus propofol for gastroscopy anesthesia in elderly patients. Scientific Reports. 2024; 14: 7645.

[10] Fan S, Zhu Y, Sui C, Li Q, Jiang W, Zhang L. Remimazolam Compared to Propofol During Hysteroscopy: A Safety and Efficacy Analysis. Pain and Therapy. 2023; 12: 695–706.

[11] Kuklin V, Hansen TG. Remimazolam for sedation and anesthesia in children: A scoping review. Acta Anaesthesiologica Scandinavica. 2024. (online ahead of print)

[12] Kimoto Y, Hirano T, Kuratani N, Cavanaugh D, Mason KP. Remimazolam as an Adjunct to General Anesthesia in Children: Adverse Events and Outcomes in a Large Cohort of 418 Cases. Journal of Clinical Medicine. 2023; 12: 3930.

[13] Chua AW, Chua MJ, Leung H, Kam PC. Anaesthetic considerations for strabismus surgery in children and adults. Anaesthesia and Intensive Care. 2020; 48: 277–288.

[14] Allahyari E, Azimi A, Zarei H, Bamdad S. Comparison of endotracheal intubation, laryngeal mask airway, and I-gel in children undergoing strabismus surgery. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences. 2021; 26: 9.

[15] Shin SY, Kim MJ, Joo J. Oculocardiac reflex and oculorespiratory reflex during strabismus surgery under general anesthesia using the laryngeal mask airway with maintenance of spontaneous respiration: A retrospective study. The Journal of International Medical Research. 2020; 48: 300060520945158.

[16] Pastis NJ, Hill NT, Yarmus LB, Schippers F, Imre M, Sohngen W, *et al*. Correlation of Vital Signs and Depth of Sedation by Modified Observer's Assessment of Alertness and Sedation (MOAA/S) Scale in Bronchoscopy. Journal of Bronchology & Interventional Pulmonology. 2022; 29: 54–61.

[17] Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology. 2007; 107: 144–152.

[18] Cao YH, Chi P, Zhou C, Lv WF, Quan ZF, Xue FS. The 50% and 95% effective doses of remimazolam tosilate with adjuvant sufentanil for sedation in patients with liver cirrhosis undergoing oesophagogastric varices screening endoscopy. Journal of Clinical Pharmacy and Therapeutics. 2022; 47: 2068–2073.

[19] Zhang K, Zhou M, Zou Z, Zhu C, Jiang R. Supraglottic

airway devices: a powerful strategy in airway management. American Journal of Cancer Research. 2024; 14: 16–32.
[20] Kim SH, Fechner J. Remimazolam - current knowledge on a new intravenous benzodiazepine anesthetic agent. Korean Journal of Anesthesiology. 2022; 75: 307–315.
[21] Chen X, Sang N, Song K, Zhong W, Wang H, Jiang J, *et al*. Psychomotor Recovery Following Remimazolam-induced Sedation and the Effectiveness of Flumazenil as an Antidote. Clinical Therapeutics. 2020; 42: 614–624.
[22] Chen S, Wang J, Xu X, Huang Y, Xue S, Wu A, *et al*. The efficacy and safety of remimazolam tosylate versus propofol in patients undergoing colonoscopy: a multicentered, randomized, positive-controlled, phase III clinical trial. American Journal of Translational Research. 2020; 12: 4594–4603.
[23] Hamdy Salman O, Gad GS, Salem AE. Sequential analysis for median effective dose of Dexmedetomidine in upper limb Lidocaine intravenous regional anesthesia. Egyptian Journal of Anaesthesia. 2020; 36: 176–183.
[24] Xiao Y, Cao Y, Pu J, Guo C, Yi Y, Deng Y, *et al*. The 50% and 95% effective dose of remimazolam tosilate for anaesthesia induction in sleep disorders patients undergoing laparoscopic cholecystectomy: an up-and-down sequential allocation trial. BMC Anesthesiology. 2024; 24: 48.
[25] Qu L, Liu M, Ouyang R, Li T, Long D, Jiang Y, *et al*. Determination of the 95% effective dose of remimazolam tosylate in anesthesia induction inhibits endotracheal intubation response in senile patients. Frontiers in Pharmacology. 2023; 14: 1136003.
[26] Gao YQ, Ihmsen H, Hu ZY, Sun W, Fang YB, Wang Z, *et al*. Pharmacokinetics of remimazolam after intravenous infusion in anaesthetised children. British Journal of Anaesthesia. 2023; 131: 914–920.
[27] Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers: Part I. Pharmacokinetics and Clinical Pharmacodynamics. Anesthesiology. 2020; 132: 636–651.
[28] Saito K, Ohno S, Maeda M, Hirata N, Yamakage M. Remimazolam anesthesia for cardiac surgery with cardiopulmonary bypass: a case report. JA Clinical Reports. 2021; 7: 21.
[29] 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. Journal of Anesthesia. 2020; 34: 543–553.
[30] Shi F, Chen Y, Li H, Zhang Y, Zhao T. Efficacy and Safety of Remimazolam Tosilate versus Propofol for General Anesthesia in Cirrhotic Patients Undergoing Endoscopic Variceal Ligation. International Journal of General Medicine. 2022; 15: 583–591.
[31] Biallas R, Rüsch D, de Decker W, Wulf H, Siebrecht D, Scholz J. Prophylaxis of postoperative nausea and vomiting (PONV) in children undergoing strabismus surgery. Sevoflurane/N2O plus dimenhydrinate vs.propofol/remifentanil plus dimenhydrinate. Der Anaesthesist. 2003; 52: 586–595.
[32] Akin A, Bayram A, Esmaoglu A, Tosun Z, Aksu R, Altuntas R, *et al*. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. Paediatric Anaesthesia. 2012; 22: 871–876.