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CLINICAL TRIAL REPORT

# Low-Dose Alfentanil Effectively Reduces the ED50 of Remimazolam for Loss of Consciousness in Pediatric Patients Undergoing General Anesthesia: A Study Using Up-and-Down Sequential Allocation Method

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**Purpose:** To investigate the effects of low-dose alfentanil on the 50% effective dose ($ED_{50}$)/95% effective dose ($ED_{95}$) of remimazolam for successful loss of consciousness during general anesthesia in pediatric patients.

**Patients and Methods:** Fifty-two pediatric patients (aged 3–12, ASA I–II) scheduled for elective surgery were divided into two groups: Group A (n=24;alfentanil 5 μg $kg^{-1}$ + remimazolam 0.1 mg $kg^{-1}$) and Group C (n=28;saline + remimazolam 0.15 mg $kg^{-1}$). The MOAA/S scale was employed for assessment. To calculate the ED50, ED95 of remimazolam for inducing loss of consciousness in pediatric patients undergoing general anesthesia. Record the monitored values (MAP, HR, $SpO_2$) at different time points and the incidence of injection pain, hiccups, spontaneous movements, hypotension, bradycardia, respiratory depression, and overall adverse events.

**Results:** In Group A, the $ED_{50}$ of remimazolam for loss of consciousness in pediatric patients was 0.212 mg $kg^{-1}$ (95% CI: 0.182 – 0.242 mg $kg^{-1}$), significantly lower than that in Group C (0.340 mg $kg^{-1}$, 95% CI: 0.295–0.388 mg $kg^{-1}$, P <0.001). Similarly, the $ED_{95}$ in Group A was 0.265 mg $kg^{-1}$ (95% CI: 0.237–0.413 mg $kg^{-1}$), significantly lower than that in Group C (0.434 mg $kg^{-1}$, 95% CI: 0.387–0.737 mg $kg^{-1}$, P <0.001). The overall incidence of adverse reactions was 8.3% in Group A, significantly lower than the 39.3% in Group C (P = 0.012). Compared with baseline values at T0, the MAP of pediatric patients in both groups decreased at T2 (P<0.05), but the reduction remained within 20% of the baseline values.

**Conclusion:** Low-dose alfentanil (5 μg $kg^{-1}$) significantly reduces the $ED_{50}$ and $ED_{95}$ of remimazolam for successful loss of consciousness during paediatric general anaesthesia induction and decreases the incidence of adverse reactions during remimazolam induced sedation.

**Keywords:** alfentanil, effective dose, general anaesthesia, paediatric, remimazolam, sedation

## Introduction

Remimazolam is a novel ultra-short-acting benzodiazepine used for sedation and induction and maintenance of general anaesthesia in adults.[1] It is rapidly hydrolyzed by non-specific tissue esterases into an inactive metabolite (CNS 7054), with rapid onset and short duration of action.[2] Alfentanil is known for its rapid onset of analgesia, short time to peak effect, and short elimination half-life, and is safe and effective in both children and adults at appropriate doses.[3,4] In a bronchoscopic sedation study, low-dose alfentanil was found to significantly decrease the required propofol induction dose and accelerate the induction onset.[5]

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In clinical anaesthesia practice, the use of a single anaesthetic agent often requires higher doses, which not only increase the risk of adverse reactions but also potentially affect patient recovery. Combining anaesthetic agents can effectively reduce the dose of a single agent, thereby lowering the incidence of adverse reactions.[6] Children have significant physiological differences from adults, and reducing anaesthesia-related adverse reactions in paediatric patients is a major challenge in clinical anaesthesia.[7] Studies have shown that the pharmacokinetics of remimazolam are similar across different age groups, including children and the elderly.[8] Studies recommend optimal remimazolam doses of 0.25–0.33, 0.19–0.25, and 0.14–0.19 mg $kg^{-1}$ for adult patients aged <40 years, 40–60 years, and 60–80 years, respectively.[9] While there is extensive research on remimazolam in adult sedation, the optimal dose for paediatric sedation and general anaesthesia induction remains to be further investigated.This study employed the modified Dixon's up-and-down method to measure the ED50, ED95, and CI for loss of consciousness induced by remimazolam combined with low-dose alfentanil (5 μg $kg^{-1}$) during general anesthesia in pediatric patients,as well as the incidence of adverse reactions, to provide clinically valuable reference data for paediatric anaesthesia induction protocols.

# Materials and Methods

## Ethical Considerations

We conducted this study in accordance with the Declaration of Helsinki.The study protocol was approved by the Ethics Committee of Weifang People's Hospital on September 12, 2024 (Ethics No. KYLL20240912-1) and registered with the Chinese Clinical Trial Registration Center on September 23, 2024 (Registration No. ChiCTR2400090045, URL: https://www.chictr.org.cn). The study was conducted in the Department of Anaesthesiology at Weifang People's Hospital from September 25 to October 15, 2024, and informed consent has been obtained from the patient's parents or legal guardians.

## Inclusion and Exclusion

Fifty-two pediatric patients scheduled for elective paediatric hernia surgery under general anaesthesia were selected. Inclusion criteria were age 3–12 years and ASA I–II. Exclusion criteria included inability to cooperate with intravenous induction, difficult airway, allergy to study drugs, developmental delay of the nervous system, or a history of preoperative sedative or analgesic use.

## Study Executeion

Pediatric patients follow a standard fasting and drinking regimen. Peripheral venous access was established in the anaesthesia preparation room. Standard monitoring in the operating room included electrocardiogram (ECG), non-invasive blood pressure (NIBP), heart rate (HR), and pulse oximetry ($SpO_2$). Pediatric patients in Group A received alfentanil 5 μg·$kg^{-1}$, while those in Group C received an equal volume of saline. One minute later, remimazolam was administered for sedation, with the dose determined by the modified Dixon sequential method and infused over one minute.

The study was designed using a modified Dixon's up-and-down sequential method. Based on previous literature[9,10] and preliminary experimental results, the initial remimazolam dose was set at 0.1 mg $kg^{-1}$ for Group A and 0.15 mg $kg^{-1}$ for Group B, with a fixed dose interval of 0.05 mg $kg^{-1}$ for both groups. Successful sedation was defined as loss of consciousness within 3 minutes after drug administration accompanied by a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of 2 (no response to loud verbal calling of name). In such cases, the subsequent patient would receive a dose reduced by one gradient level. To minimize interference and ensure accurate sedation assessment, the sedation level was evaluated every 30 seconds. If the MOAA/S score failed to reach 2 within 3 minutes, the case was considered a sedation failure, and the next patient would receive a dose increased by one gradient level. The study was terminated when seven crossover points (Loss of consciousness turns from success to failure) were observed.

For children who achieved successful loss of consciousness, intravenous sufentanil and cisatracurium were administered. Following successful anesthetic induction, a laryngeal mask airway was inserted. In cases where loss of consciousness failed, rescue sedation was provided via intravenous propofol bolus (1–2 mg $kg^{-1}$). Once vital signs stabilized and the MOAA/S score reached 2, the same doses of sufentanil (0.5 μg $kg^{-1}$) and cisatracurium (0.2 mg $kg^{-1}$) were administered intravenously, with LMA insertion performed after successful induction.

Mechanical ventilation was maintained to keep end-tidal carbon dioxide ($ETCO_2$) between 35–45 mmHg. Starting from 1 minute after LMA placement, anesthesia was maintained with 3% sevoflurane inhalation, with adjustments made to ensure adequate anesthetic depth throughout the procedure.

If bradycardia (heart rate < 70 bpm) or hypotension (systolic blood pressure < 70 mmHg + [2 × age]) occurred, atropine or ephedrine was administered for symptomatic treatment. For respiratory depression (RR < 10 breaths/min or $SpO_2$ < 90% lasting >1 min), initial management included jaw thrust and mask-assisted ventilation. If mask ventilation proved ineffective, immediate insertion of a laryngeal mask airway or endotracheal intubation was performed to establish controlled ventilation. All anesthetic procedures were conducted by the same team of anesthesiologists.

## Randomization and Blinding

Based on previous studies,[9,11] it was predicted that approximately 30 patients per group would be needed to reach 7 inflection points, totaling 60 patients. A researcher used SPSS 25.0 software to generate 60 random numbers for random assignment at a 1:1 ratio into Groups A and C. Patients were assigned to groups based on their enrollment order. When one group reached 7 inflection points first, enrollment was stopped, and the other group continued until the required number was reached.

The study drugs were prepared by an anaesthesiology nurse who was familiar with the protocol and aware of patient assignments. Alfentanil (5 μg $kg^{-1}$) or saline was diluted to 10 mL in identical syringes and labeled similarly. The attending anaesthesiologist, who was unaware of the specific study drug, administered the anaesthesia. The patients were also unaware of the specific drugs used. The assessment and data collection of the MOAA/S score was performed by an independent anesthesiologist assistant who was blinded to the grouping.

## Observation Indicators

The primary outcome measures included the $ED_{50}$ and $ED_{95}$ of remimazolam for loss of consciousness in pediatric patients undergoing general anesthesia in pediatric patients, along with their 95% confidence intervals, which were compared between the two groups, while secondary outcomes encompassed monitored parameters (MAP, HR, and $SpO_2$) at before anesthesia induction (T0), alfentanil or equivalent saline was given for 1 min (T1) and remimazolam was injected for 2 min (T2), as well as the incidence of injection pain (limb movement during remimazolam bolus), hiccups (involuntary myoclonic contractions of diaphragm/intercostal muscles with characteristic "hic" sound from glottis closure), spontaneous movements (unstimulated involuntary motions post-remimazolam), hypotension (SBP < 70 mmHg + [2×age]), bradycardia (HR < 70 bpm), respiratory depression (RR < 10 breaths/min or $SpO_2$ < 90% for >1 min), and overall adverse events.

## Statistical Analysis

The statistical analysis was performed using SPSS 25.0 software. To see how our data was distributed, we ran it through the Shapiro–Wilk test. For data that followed a normal distribution, we reported the mean and standard deviation. If the data did not follow a normal distribution, we used the median and interquartile range. For counts, we just used percentages. When comparing groups, we used chi-square tests, Fisher's exact tests, or rank-sum tests, depending on what made sense for the data. To figure out the $ED_{50}$ and $ED_{95}$ (the doses that worked for 50% and 95% of the paediatric patients, respectively) for remimazolam, we used probit regression analysis for both Group A and Group C. We compared the $ED_{50}$ and $ED_{95}$ values between the two groups using the Mann–Whitney *U*-test. We made sequential graphs and dose-response curves using GraphPad Prism 10 software. Any p-value less than 0.05 meant the difference was statistically significant.

# Results

## General Information on the Paediatric Patients

We had 24 paediatric patients in Group A and 28 in Group C. When we looked at their ages, BMI, and ASA classifications, there were not any significant differences between the groups (Table 1).

**Table 1** Comparison of General Data Between the Two Groups

| | Group A n=24 | Group C n=28 | *P* |
|---|---|---|---|
| Age (yr) | 6(2.47) | 5.64(1.93) | 0.569 |
| Weight (kg) | 20.75(18.09–29.13) | 20.00(18.38–26.75) | 0.956 |
| Height (cm) | 119.50(107.75–133.75) | 119.00(111.5–130) | 0.949 |
| BMI (kg $m^{-2}$) | 15.44(14.44–16.71) | 15.04(14.32–16.77) | 0.463 |
| ASA physical status | | | |
| I | 15(62.5) | 18(64.3) | 1.000 |
| II | 9(37.5) | 10(35.7) | 1.000 |

**Notes**: Data are expressed as median (inter-quartile range), or number (percentage).
**Abbreviations**: BMI, body mass index; ASA, American Society of Anesthesiologists status.

## Sequential Experiment Results

In Group A, we hit 7 inflection points (Loss of consciousness turns from success to failure) with 24 paediatric patients (11 positive responses, 13 negative). In Group C, it took 28 paediatric patients to get those 7 inflection points (13 positive, 15 negative). The modified Dixon sequential plots illustrating remimazolam administration for general anesthesia induction in pediatric patients from both groups are presented in Figure 1.

## Dose-Response Relationship

Using probit regression, we found that Group A's $ED_{50}$ and $ED_{95}$ for remimazolam were 0.212 mg $kg^{-1}$ (95% CI: 0.182–0.242 mg $kg^{-1}$) and 0.265 mg $kg^{-1}$ (95% CI: 0.237–0.413 mg $kg^{-1}$), respectively. For Group C, the values were 0.340 mg $kg^{-1}$ (95% CI: 0.295–0.388 mg $kg^{-1}$) and 0.434 mg $kg^{-1}$ (95% CI: 0.387–0.737 mg $kg^{-1}$). Group A needed significantly less remimazolam for both $ED_{50}$ and $ED_{95}$ compared to Group C ($p < 0.05$). The dose-response curves for both groups are in Figure 2.

## Vital Signs Comparison

A comparative analysis of hemodynamic parameters revealed a statistically significant reduction in mean arterial pressure (MAP) at T 2 relative to baseline values (T0) in both pediatric cohorts (P<0.05), with the magnitude of decrease remaining clinically acceptable (<20% of baseline). No significant temporal variations in heart rate (HR) or oxygen saturation ($SpO_2$) were observed between groups throughout the monitoring period (P>0.05). Complete numerical data are presented in Table 2.

## Adverse Reactions

In Group A, 2 paediatric patients (8.3%) had adverse reactions during anaesthesia induction—one had spontaneous movements, and one had respiratory depression. All issues were resolved with follow-up anaesthesia drugs or simple

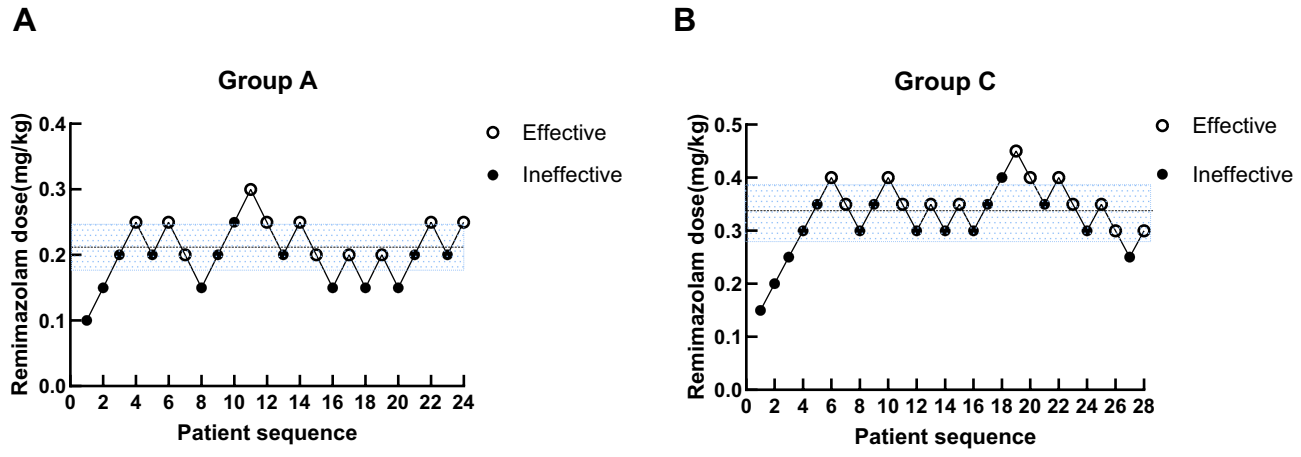


**Figure 1** Individual response to intravenous remimazolam at a corresponding dose (mg $kg^{-1}$), (**A**) Group A received remimazolam in combination with alfentanil, and (**B**) Group C received remimazolam and saline.Open circles represent successful loss of consciousness induction, whereas solid circles denote failed loss of consciousness induction. The shaded area includes the ED50 value (shown as a thicker dashed line) with its 95% confidence interval.

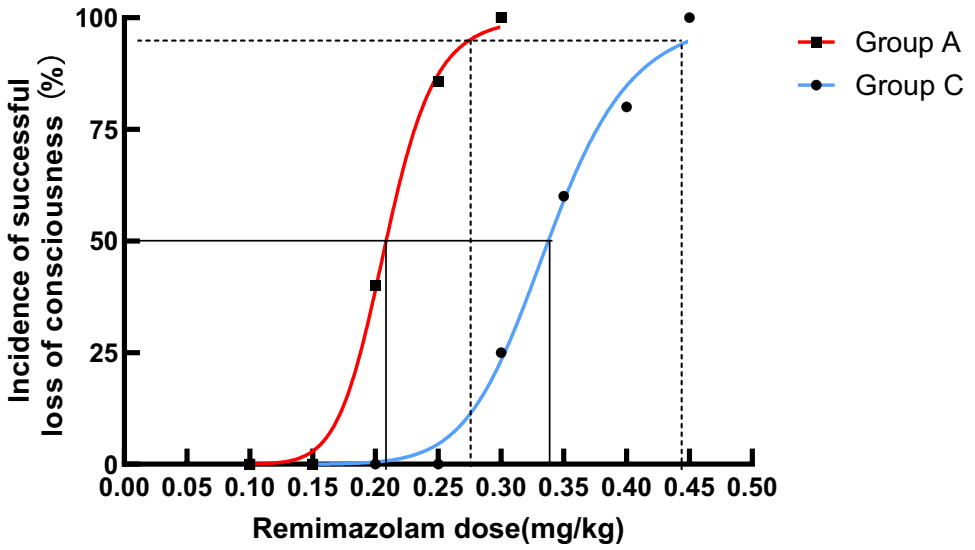


**Figure 2** Dose-response curves of intravenous remimazolam for anesthesia sedation plotted from estimated probabilities of effective response (1 to 100%) vs the corresponding dose of the initial bolus derived from probit regression analysis. Utilizing probit regression, The $ED_{50}$ and $ED_{95}$ values for Group A were 0.212 mg $kg^{-1}$ (95% CI: 0.182–0.242 mg $kg^{-1}$) and 0.265 mg $kg^{-1}$ (95% CI: 0.237–0.413 mg $kg^{-1}$), respectively. For Group C, the $ED_{50}$ and $ED_{95}$ values were 0.340 mg $kg^{-1}$ (95% CI: 0.295–0.388 mg $kg^{-1}$) and 0.434 mg $kg^{-1}$ (95% CI: 0.387–0.737 mg $kg^{-1}$), respectively. The solid line represents the $ED_{50}$ value, and the dashed line represents the $ED_{95}$ value.

interventions like jaw thrust and mask ventilation. No paediatric patients had hiccoughs, hypotension, bradycardia, or injection pain. In Group C, 11 paediatric patients (39.3%) had adverse reactions—4 had hiccoughs, 6 had spontaneous movements, and 1 had hypotension. All resolved on their own after follow-up drugs. No paediatric patients had bradycardia, respiratory depression, or injection pain. The overall incidence of adverse reactions was significantly lower in Group A ($p < 0.05$). The details are in Table 3.

**Table 2** Comparison of Vital Signs of Pediatric Patients Between the Two Groups

| | | T0 | T1 | T2 | *P* |
|---|---|---|---|---|---|
| MAP | Group A n=24 | 88.00±9.97 | 83.46±9.17 | 73.96±9.26[a] | 0.000 |
| | Group C n=28 | 85.21±13.04 | 85.18±13.02 | 76.00±9.00[b] | 0.006 |
| HR | Group A n=24 | 95.04±19.32 | 90.58±14.66 | 92.21±11.04 | 0.612 |
| | Group C n=28 | 97.25±17.28 | 96.89±16.83 | 101.00±12.71 | 0.571 |
| $SpO_2$ | Group A n=24 | 98(98.00,99.00) | 98(97.00,99.00) | 97(96.75,99.00) | 0.072 |
| | Group C n=28 | 98(97.75,99.25) | 99(98.00,100.00) | 99(98.00,100.00) | 0.903 |

**Notes**: Data are expressed as M ± SD, median (interquartile range), Compared with T0, the [a]*P*= 0.000. Compared with T0, the [b]*P*= 0.005; (T0): Before anesthesia induction. (T1): Alfentanil or equivalent saline was given for 1 min. (T2): remimazolam was injected for 2 min.

**Table 3** Adverse Reactions

| | Group A n=24 | Group C n=28 | *P* |
|---|---|---|---|
| Hiccups | 0(0) | 4(14.3) | 0.115 |
| Spontaneous movements | 1(4.2) | 6(21.4) | 0.107 |
| Injection pain | 0(0) | 0(0) | – |
| Hypotension | 0(0) | 1(3.6) | 1.000 |
| Bradycardia | 0(0) | 0(0) | – |
| Hypoxemia | 1(4.2) | 0(0) | 0.462 |
| Total adverse reactions | 2(8.3) | 11(39.3) | 0.012* |

**Notes**: Data are expressed as number (percentage). *Significance difference in comparison with control group (P=0.012).


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## Discussion

The present study demonstrated that the $ED_{50}$ and $ED_{95}$ of remimazolam for successful loss of consciousness were 0.212 mg $kg^{-1}$ (95% CI: 0.182–0.242 mg $kg^{-1}$) and 0.265 mg $kg^{-1}$ (95% CI: 0.237–0.413 mg $kg^{-1}$) in Group A, compared to 0.340 mg $kg^{-1}$ (95% CI: 0.295–0.388 mg $kg^{-1}$) and 0.434 mg $kg^{-1}$ (95% CI: 0.387–0.737 mg $kg^{-1}$) in Group C, respectively. Coadministration with alfentanil resulted in 37.6% and 38.9% reductions in the $ED_{50}$ and $ED_{95}$ of remimazolam in Group A relative to Group C, consistent with the well-established potentiating effect of opioids on sedative anesthesia.[12,13] These findings indicate that the median effective induction dose for pediatric patients aged 3–12 years was 0.340 mg $kg^{-1}$ as a single bolus, with only mild adverse effects observed within 3 minutes post-administration. Importantly, concurrent administration of alfentanil 5 μg $kg^{-1}$ significantly reduced the effective dose of remimazolam required for successful loss of consciousness while simultaneously decreasing the overall incidence of adverse events.

This study comparatively evaluated the efficacy of remimazolam monotherapy versus remimazolam-alfentanil combination (5 μg $kg^{-1}$) for inducing loss of consciousness in pediatric patients, specifically designed to characterize both the intrinsic sedative properties of remimazolam and its pharmacodynamic potentiation by opioid coadministration. Research by Chae et al[9] demonstrated that the ED50 and ED95 of remimazolam for inducing loss ofconsciousness in adults were 0.11 mg $kg^{-1}$ and 0.14 mg $kg^{-1}$, respectively. They recommended optimal doses of 0.25–0.33 mg $kg^{-1}$, 0.19–0.25 mg $kg^{-1}$, and0.14–0.19 mg $kg^{-1}$ for patients youngerthan 40 years,60–80 years, and olderthan 80 years, respectively. A study onremimazolam in female patients foundthe ED50 and ED95 for loss of consciousness to be 0.175 mg $kg^{-1}$ and 0.255 mg $kg^{-1}$.[10] while our findings indicate that the optimal dose for inducing loss of consciousness in pediatric patients is significantly higher than that in adults, suggesting that directly applying adult dosages to children may be insufficient, which could be related to the relatively larger total fluid volume in younger children.[14] This study observed that, compared to the baseline values at T0, the MAP of children in both groups decreased at T2, but the reduction remained within 20% of the baseline; additionally, there were no significant differences in HR and $SpO_2$ between the two groups over time, indicating that remimazolam has minimal impact on respiratory and circulatory functions.Previous studies have shown that remimazolam is non-inferior to propofol for induction and maintenance of general anesthesia in children, with stable hemodynamics and a low incidence of adverse effects.[15] Pharmacokinetic studies in pediatric patients have revealed that remimazolam exhibits high clearance, a small volume of distribution, and a short half-life, with pharmacokinetics similar to those in adults.[16] Therefore, remimazolam is a promising agent for pediatric anesthesia, offering minimal hemodynamic impact and excellent controllability. This suggests that an appropriate dose of remimazolam would be a favorable choice for induction sedation in children.

When combined with alfentanil, the overall incidence of adverse effects in pediatric patients decreased, though no statistically significant difference was observed in individual adverse events—a finding that may be attributed to alfentanil reducing the required dose of remimazolam. The adverse effects of alfentanil are dose- and effect-site concentration-dependent, primarily mediated by its μ-opioid receptor agonist activity, with respiratory depression being the most clinically relevant, while hemodynamic disturbances rarely occur.[17] The single case of respiratory depression observed in Group A may be related to the use of opioids. A meta-analysis on alfentanil in bronchoscopy also demonstrated that supplemental alfentanil helps reduce cough scores and propofol dosage but increases the risk of hypoxemia.[18] When opioids are combined for induction, close patient monitoring should be exercised to be vigilant for the onset of respiratory depression.

Studies have shown that opioids not only provide significant analgesic effects but also induce a deep sedative state in humans, during which the brain exhibits characteristics similar to those observed under anesthesia or sleep. Electro-corticographic monitoring reveals patterns closely resembling reduced brain arousal.[19,20] This property explains why pre-administration of opioids can reduce the required dose of remimazolam and help patients achieve the desired sedation level more quickly for surgery. Huang XD et al[19] found that when remimazolam was combined with fentanyl in elderly female patients, the $ED_{50}$ and $ED_{95}$ for loss of consciousness were significantly lower compared to remimazolam alone. This indicates that co-administration of opioids markedly reduces the $ED_{50}$ of remimazolam for inducing unconsciousness in elderly female patients—a trend consistent with our findings in pediatric anesthesia.Compared with sufentanil, alfentanil provides more stable hemodynamics during anesthesia induction, with fewer adverse effects such as injection pain, demonstrating higher safety and reliability.[21] The results of this study also confirm that alfentanil has minimal circulatory depressant effects. Compared with the remimazolam-alone

group, there were no statistically significant differences in heart rate or $SpO_2$ changes before and after drug administration. Compared with the basal value at T0, the MAP of the children in the two groups was reduced at T2, but the decrease was within 20% of the basal value. Combined with clinical experience, this may be acceptable to most anesthesiologists.

Our study has several limitations. First, the included children aged 3–12 years span a wide developmental range with distinct age-related differences, yet no age-stratified analysis was performed. Second, this study was confined to relatively healthy ASA I–II pediatric patients undergoing elective surgery, necessitating further research on higher-risk populations. Finally, as this was a single-center study, multi-center trials are required to validate the findings.

## Conclusion

In summary, this study confirmed that low-dose alfentanil (5 μg $kg^{-1}$) significantly reduces the $ED_{50}$ and $ED_{95}$ of remimazolam for successful loss of consciousness during paediatric general anaesthesia induction and decreases the incidence of adverse reactions during remimazolam induced sedation. Further multicenter studies are warranted before widespread implementation.

## Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the first author on reasonable request.

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## 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 author(s) report no conflicts of interest in this work.

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