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The Effect of Remimazolam Anesthesia on Patients undergoing Elective Surgery in Iraq

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ABSTRACT: Background: Optimizing pediatric sedation remains challenging due to developmental variability in drug response. While the ultra-short-acting benzodiazepine remimazolam offers superior hemodynamic stability and predictable esterase-based metabolism, its clinical application is limited. To address this, rigorous dose-finding studies are essential to establish the 95% effective dose, ensuring safer and more standardized anesthetic protocols for children.

Methods: This was a prospective, age-stratified, single-center dose-finding study. This study was conducted on children undergoing elective surgery. Patients were stratified into two age groups based on predefined age criteria: preschool and school-aged children. The initial intravenous dose of remimazolam was 0.2 mg/kg, followed by a subsequent 0.05 mg/kg dose administered through a sequential ascending-descending method based on the patient's response. Vital signs and recovery outcomes were monitored throughout the procedure. The ED95 was estimated using isotonic regression with bootstrap confidence intervals, and statistical analyses were performed using appropriate nonparametric and mixed-effects methods.

Results: This study included 80 children (40 preschoolers, 40 school-aged). Remimazolam demonstrated predictable hemodynamic effects with group-specific heart rate responses. The estimated ED95 was 0.389 mg/kg for preschoolers and 0.362 mg/kg for school-aged children. Adverse events were rare and transient. While anesthesia and operation times were similar, preschoolers experienced significantly longer wake-up times ($P<0.001$).

Conclusion: Remimazolam provides safe and effective sedation for elective pediatric surgery, with predictable hemodynamic responses and a favorable safety profile. While the estimated ED95 varies slightly between preschool and school-aged children, both groups achieve adequate sedation.

BACKGROUND

A major challenge in anesthesiology practice is providing safe and effective anesthetic for patients having a surgery [1]. Anesthetic dosage adjustments are frequently required to mitigate adverse outcomes and ensure rapid post-operative recovery. This challenge is amplified in pediatric settings, where anatomical and physiological immaturity significantly alters drug sensitivity and clearance rates, increasing the susceptibility to side effects like bradycardia or airway obstruction [2]. Therefore, fast-acting, short-duration anesthetics with a high safety record are prioritized when choosing anesthetics for children [3].

Remimazolam is a new benzodiazepine with a relatively short half-life. When given intravenously, its pharmacokinetic characteristics include hemodynamic stability, minimal respiratory depression [4], quick beginning and termination of activity, and no irritating effects. Unlike traditional agents that rely heavily on hepatic or renal clearance, the esterase-based

metabolism of remimazolam offers a more predictable pharmacological profile across diverse patient populations [5]. This unique metabolic pathway minimizes the risk of prolonged sedation, a common complication with benzodiazepines like midazolam, especially in patients with impaired organ function. Consequently, remimazolam has become a viable option for sedating school-age children [6].

A main barrier to its wider use is the lack of evidence-based, age-specific recommended dose [7]. The optimal dose may, thus, be variable [8]. This variability is often exacerbated by the rapid physiological and metabolic maturation processes inherent in the pediatric population, which necessitates highly precise titration to achieve the target depth of sedation [3]. Furthermore, there is a paucity of data addressing whether adult-derived dosing guidelines can be safely extrapolated to children, highlighting a significant knowledge gap in pediatric pharmacology. Therefore, well-designed dose-determining studies are essential for developing appropriate dosing strategies. Rigorous clinical investigation is required to define the therapeutic index, ensuring that the transition from empirical dosing to evidence-based practice is achieved. Establishing such benchmarks is critical not only for optimizing patient safety but also for standardizing clinical care protocols in resource-limited or high-volume surgical settings, such as those found in Iraq. The primary objective of this study is to determine the 95% effective dose of remimazolam required to achieve adequate anesthesia in children.

METHODS

This was a prospective, age-stratified, single-center dose-finding study designed to estimate the ED95 of remimazolam in children undergoing elective surgery. Patients were stratified into two age groups based on predefined age criteria: preschool and school-aged children. The present pilot study received Ethics Committee approval code: (BU/COP/2026/001) in 10/03/2026. The study was completed in the first half of 2026. Written informed consent was obtained from all participants. The experiment adhered to the provisions of the Declaration of Helsinki [9], in judging the eligibility of children undergoing elective surgery. The exclusion criterion was a pre-known allergy to remimazolam.

Dosage:

The effective dose of remimazolam was estimated following a progressive ascending-descending experimental design. A fixed dose increase of 0.05 mg/kg was used, and the dose given to each subsequent patient was determined based on their response to anesthesia [10]. If the dose for the next patient was increased by 0.05 mg/kg, s/he would receive the same dose with a probability of 0.95, or it would be decreased by 0.05 mg/kg with a probability of 0.05 [11].

Anesthesia protocol:

Preschoolers and schoolers made up the two age groups of participants. Clear liquids were prohibited for two hours and solids for four to eight hours, in accordance with standard preoperative fasting protocols [12]. To allow for parental presence, intravenous fluids were given before the anesthesia, and cannulas were placed prior to the beginning of the preoperative procedure. Important vital indicators were noted, such as non-invasive blood pressure, heart rate, and oxygen saturation. Patients were positioned supine in the operating room while non-invasive blood pressure, electrocardiogram (ECG), oxygen saturation, and end-expiratory carbon dioxide were continuously monitored. Prior to the administration of remimazolam, patients received 100% of oxygenation.

The remimazolam was given as a single intravenous dose after dilution in 0.9% of saline [13]. The BCD algorithm was used to predict successive doses for pediatric patients after the initial dose of 0.2 mg/kg. The Modified Awareness and Anesthesia Rating Scale (MOAA/S) [14] was used to measure anesthesia. Three minutes after the drug was administered, a score of < 3 indicated effective anesthesia. The treatment included continuing doses if any negative reactions were observed. Sevoflurane was used as a last resort if the anesthesia failed.

While sevoflurane, sufentanil, and cisatracurium were used to produce anesthesia, vital signs were maintained within 20% of the baseline [15]. Recovery phases, adverse effects, and the onset of anesthesia were all noted. Wake-up time was defined as the interval between the end of surgery and recuperation, denoted by a MOAA/S score of at least five. A systolic blood pressure of less than 70 mmHg plus twice the patient's age in years is considered hypotension. Age-specific bradycardia thresholds are less than 60 mmHg for school-age children and less than 80 mmHg for preschoolers [16]. Vasopressors or anticholinergics may be used to treat episodes of bradycardia or hypotension.

Statistical analysis

Based on simulation recommendation to 20–40 subjects, 40 patients per age group were included to estimate the ED_{95} via isotonic regression (PAVA). Confidence intervals were calculated using a 1,000-iteration bias-corrected percentile bootstrap.

Continuous and categorical variables were analyzed using Kruskal–Wallis (with post hoc Mann–Whitney U) and Fisher's exact tests, respectively, with effect sizes by Cramér's V. Time-dependent hemodynamic changes were modeled using a generalized linear mixed-effects Gamma model. Multiple comparisons were adjusted using Bonferroni correction. All analyses were done in SPSS (v28.0) and R (v3.6.2) with the significance set at $P < 0.05$.

RESULTS

Each age group included 40 participants, totaling 80 young subjects in the cohort. Table 1 provides a summary of baseline demographic characteristics. As expected, the schooler group (n=40) was significantly older and heavier (mean age of 7.0 years, weight of 23.5 kg) than the preschooler group (n=40, mean age of 4.0 years, weight of 18.5 kg). There was a significant difference in sex distribution between the two groups at baseline. The preschooler group was predominantly female (70.0%), while the schooler group was predominantly male (80.0%). Both groups consisted entirely of patients classified as ASA Class I and II, although the preschooler group had a higher proportion (75.0%) of Class II patients than the schooler group (60.0%). Table 1 shows the changes from baseline (T0) to one minute after remimazolam administration (T1) and three minutes after remimazolam administration (T2). The preschooler group started with a higher baseline heart rate (106 bpm) and showed a slight, steady decrease over time (106 → 104 → 102 bpm). In contrast, the schooler child group began with a lower rate (88 bpm) but experienced a marked increase at T1 (100.5 bpm) before decreasing slightly at T2 (94 bpm). Both groups showed a slight, gradual decrease in blood pressure from T0 to T2 after remimazolam administration.

Preschooler group: 70 → 68 → 66.5 mmHg

Schooler group: 80 → 76 → 74 mmHg

Remimazolam appears to produce small and predictable decreases in blood pressure in both groups, but it induces different initial heart rate responses between preschool children (slight slowing) and school-age children (transient acceleration).

Table 2 shows the relationship between the dose of and response to remimazolam in the two age groups and the PAVA-adjusted sedation response rates. The reaction rate for preschoolers peaks between the doses of 0.25 and 0.35 mg/kg, with 0.35 mg/kg producing a perfect response rate (1.000, 11/11 sedated). The fluctuations are smoothed out by the PAVA-adjusted response rate, which increases steadily from 0.212 at the lowest dose (0.20 mg/kg) to a peak probability of 0.985 at 0.35 mg/kg before dramatically falling at 0.45 mg/kg. At a narrower, slightly lower sweet spot concentrated intensively at 0.30 mg/kg, schoolers achieve a perfect crude response rate (1.000, 26/26 sedated). The PAVA-adjusted model shows that a high modeled probability at 0.25 mg/kg (0.940) is closely followed by the highest probability of response at 0.30 mg/kg (0.973). There is a very uneven distribution of samples across doses. For example, the 0.30 mg/kg cohort (n= 26) dominates the schooler group findings, although other extreme dose levels (such as 0.20 and 0.40/0.45 mg/kg) include only 1 or 2 cases, making their crude "0.000" rates statistically unstable. Here, the PAVA (Pool-Adjacent-Violators Algorithm) adjustment plays a crucial role in correcting for these minor sample anomalies (e.g., converting a 0/1 crude success at 0.20 mg/kg into a more realistic modeled probability of 0.511 for schoolers based on the data). The estimated ED_{95} of remimazolam was 0.389 $mg•kg^{-1}$ (95% CI: 0.258–0.440) in preschoolers aged 3.5–5.5 yrs , and 0.362 $mg•kg^{-1}$ (95% CI: 0.228–0.396) in school-aged 6.5-9-year participants.

Table 3 summarizes the adverse events that occurred within three minutes of taking remimazolam. One patient (0.8% of the total) in the schooler group had hypotension. There was no significant difference in the incidence of hypotension between the two age groups. The effect size estimated for the preschooler group and schooler group is 0.130 (0.112-0260) for hypotension and 0.352 (0.211-0.479) for bradycardia. Following the administration of a single dose of a vasoactive drug, all bouts of bradycardia and hypotension were resolved. The data show that preschoolers have a statistically slower wake/emergency time than schoolers, despite the fact that remimazulam offers both groups a similar quick onset and a high safety profile (fewer adverse events).

The perioperative characteristics were compared between the two groups. The two groups did not significantly differ in terms of sedation onset time, operation duration, and the total anesthetic time ($P > 0.05$), and the corresponding effect sizes were small. P-value for the perioperative data was 0.343 for the sedation onset time, 0.110 for the operation time , 0.223 for anesthesia duration, and <0.001 for the wake-up time for preschoolers and schoolers.

DISCUSSION

A BCD algorithm was used to predict the subsequent doses for pediatric patients following the initial dose of 0.2 mg/kg of remimazolam needed to provide appropriate sedation in patients undergoing surgery. The estimated ED_{95} of remimazolam was 0.389 mg•kg^{-1} (95% CI: 0.258–0.440) in preschoolers aged 3.5–5.5 yrs, and 0.362 mg•kg^{-1} (95% CI: 0.228–0.396) in schoolers aged 6.5-9 yrs. Remimazolam generally showed satisfactory safety and anesthetic efficacy in both age groups. However, it should be administered cautiously because of the apparent physiological sensitivity in young infants. An effective and safe level of preoperative anesthesia for patients undergoing surgery is shown by a MOAA/S score of < 3. A MOAA/S score of ≤ 3 was selected as the criterion for effective anesthesia since the short surgical procedures carried out in this study, including inguinal hernia repair, required a quick onset of anesthesia and recovery.

It is noteworthy that different studies have reported different remimazolam dose requirements, mostly because of various anesthetic characteristics. For instance, the deeper depth of anesthesia needed in one trial is probably the reason for the greater dose requirements. This proximity is probably because the same anesthetic value (MOAA/S < 3) [17], was used, even though this class has different physiological traits. These findings show a significant correlation between remimazolam dosage and anesthesia level, with greater doses needed for deeper anesthesia. This comparison shows how context-dependent the effective dosage of remimazolam is.

According to recent pharmacokinetic research, remimazolam has a steady-state half-life of around 2.7 minutes, and reaches the peak effect about 2.5 minutes after ingestion. A 3-minute observation time was selected because this research only used a single dosage. The BCD method improves dose estimation accuracy by offering a practical approach for predicting the target doses. The success rate of anesthesia remained continuously high, with PAVA-adjusted response rates exceeding 98.9% at a dose of 0.45 mg/kg, though the children had higher ED_{95} values. These findings support the accuracy and dependability of BCD methodology.

Remimazolam usage has been linked to a brief elevation in heart rate in adults [18]. Overall HR did not show any significant time-dependent changes in this research (Table 1). However, the incidence of bradycardia was significantly higher in preschoolers than schoolers (Table 3). Previous studies using various sedatives found a correlation between masculinity and higher prevalence of bradycardia during pediatric sedation [19]. To validate these findings and unravel the mechanisms underlying bradycardia in this age range, more extensive research is required.

In line with the existing literature on adults, remimazolam did not cause clinically significant hemodynamic instability in the young population. These changes were insignificant and unlikely to have any therapeutic effect, even though MAP had statistically significant temporal effects. Previous pediatric studies that used remimazolam for anesthetic induction did not show any signs of respiratory depression [20].

There were no significant differences between the two age groups in this trial with regard to the onset of action (Table 3). Remimazolam onset times were found to be greater in earlier studies using a MOAA/S score of ≤ 1 [21]. Onset times similar to those shown here have been reported in studies using a MOAA/S threshold of < 3 [22]. These findings suggest that remimazolam provides a quick onset of effect for pediatric surgeries requiring mild sedation. Compared to the schooler group, preschoolers had significantly longer wake-up times (Table 3). A variety of complicating factors likely affect the wake-up time, such as the combined effects of several anesthetic medicines and the more cautious post-anesthesia care protocols often used for younger children at our institution [23].

The usefulness of BIS monitoring in this context is limited by the unclear association between BIS levels and remimazolam sedative effectiveness. Similarly, there is only a weak relationship between MOAA/S scores and the Narcotrend Index [24], rendering it unsuitable for a reliable assessment of sedation depth during remimazolam administration.

Both groups achieved sedation remarkably fast and at almost identical rates. Preschoolers had a median onset of 38.5 seconds compared to 38.0 seconds for schoolers (P = 0.343), indicating that the drug acts at an equal speed regardless of the age brackets. Schoolers had slightly longer median operation times (15.0 vs. 11.5 min) and anesthesia times (23.5 vs. 20.5 min), though these differences did not reach statistical significance (P = 0.110 and P = 0.223, respectively). Wake-up time: This is the most clinically significant procedural finding. Preschoolers took significantly longer to wake up (median 17.5 minutes) than schoolers (median 16.0 minutes). This difference is highly statistically significant (P < 0.001) with a notable effect size (0.391).

Limitations of study: Only healthy children categorized as Class I or II by the American Society of Anesthesiologists (ASA) were included in the analysis of findings. As a result, children categorized as Class III or higher may not be directly affected by the estimated effective dosage (ED_{95}) values.

CONCLUSION

This study successfully determined the preliminary effective dose 95% (ED95) of remimazolam for achieving adequate sedation (defined as MOAA/S score ≤ 3) in pediatric patients undergoing elective surgery in Iraq. Our findings indicate that the ED95 was 0.389 mg/kg0.389 mg/kg (95% CI: 0.258–0.4400.258–0.440) for preschool-aged children and 0.362 mg/kg (95% CI: 0.228–0.3960.228–0.396) for school-aged children. The results demonstrate that remimazolam is effective in providing adequate anesthesia across both age groups, with no statistically significant differences observed in the onset of sedation or duration of anesthesia (P>0.05). Furthermore, the drug exhibited a generally good safety profile, characterized by infrequent and transient adverse events such as mild hypotension or bradycardia, which responded well to minor interventions. A key finding was the significantly longer wake-up time observed in the preschooler group compared to the school-aged group (P<0.001). This suggests a potential difference in the drug's recovery profile or the underlying physiological recovery mechanisms in younger children. Therefore, while remimazolam proves to be a safe and effective anesthetic agent in pediatric populations, the age-specific ED95 values and the observed difference in recovery times highlight the importance of age-tailored dosing and vigilant post-anesthetic monitoring, particularly in younger children, to optimize patient outcomes and ensure a smooth recovery process.

What is already known on this topic

1. Optimizing sedation in children is inherently difficult due to developmental variability in how they respond to drugs.

2. Remimazolam is an ultra-short-acting benzodiazepine that offers superior hemodynamic stability and predictable, esterase-based metabolism.

3. There is a lack of age-specific guidelines for remimazolam in pediatric care, making rigorous dose-finding studies necessary to establish standardized, safe protocols (specifically the 95% effective dose, or ED95).

What this study adds

1. It establishes the precise 95% effective dose (ED95) of remimazolam for two distinct pediatric cohorts using rigorous isotonic regression: 0.389 mg/kg for preschool-aged children and 0.362 mg/kg for school-aged children.

2. It reveals crucial post-sedation differences between age groups, specifically demonstrating that despite receiving similar relative doses, preschool children experience significantly longer wake-up times (P < 0.001) than school-aged children.

3. It provides actionable safety and efficacy data that can be used to develop standardized, age-stratified pediatric guidelines and optimize post-anesthetic recovery monitoring for younger cohorts.

Ethics Approval and Consent to Participate

Ethical clearance and approval were granted from the Research Ethics Committee in the College of Pharmacy, Al-Bayan University (No BU/COP/2026/001 in 10/03/2026). This was in concordance with the 1964 Declaration of Helsinki.

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Author Contributions

The author participated in all aspects of the study.

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Competing interests

The authors declare no competing interests.

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Tables

Table 1. Demographic and baseline clinical characteristics of preschool and school-aged children undergoing elective surgery at a single-center hospital in Iraq (N = 80)

Patients' data	Preschoolers (n=40)	Schoolers (n=40)
Age (yrs)	4.0 (3.5–5.5)	7.0 (6.5–9.0)
Weight (kg)	18.5 (14.5-23)	23.5 (20.0–34.0)
Sex		
Male	12 (30.0)	32 (80.0)
Female	28 (70.0)	8 (20.0)
ASA physical status, n (%)		
I	10 (25.0)	16 (40.0)
II	30 (75.0)	24 (60.0)
Heart Rate (bpm)		
T0	106 (95-119)	88 (82.5-108)
T1	104 (102.5-115)	100.5(89-116)
T2	102 (93-106)	94 (90-110)
Blood Pressure(mmHg)		
T0	70 (68-78)	80(74-84)
T1	68(66-74)	76(70-82)
T2	66.5(63-70)	74(68-80)

American Society of Anesthesiologists (ASA), or number (%)

T0 baseline, T1 one min post remimazolam, T2 3 min post remimazolam

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Table 2. Response rates to remimazolam at sequential dose levels used for pooled adjacent violators algorithm (PAVA) analysis to estimate the ED95 in preschool and school-aged children undergoing elective surgery in Iraq (N = 80)

Assigned dose (mg·kg^{-1})	No. sedated	No. tested	Response rate	PAVA-adjusted response rate
Preschoolers				
0.20	0	1	0.000	0.212
0.25	13	14	0.928	0.890
0.30	3	4	0.751	0.725
0.35	11	11	1.000	0.985
0.40	7	8	0.873	0.961
0.45	1	2	0.501	0.462
Schoolers				
0.20	0	1	0.000	0.511
0.25	2	3	0.665	0.940
0.30	26	26	1.000	0.973
0.35	8	9	0.887	0.720
0.40	0	1	0.000	0.863

PAVA pool-adjacent-violators , and No= Number.

Table 3. Perioperative outcomes and adverse events in preschool and school-aged children undergoing elective surgery with remimazolam anesthesia at a single-center hospital in Iraq (N = 80)

Parameters	Preschoolers (n=40)	Schoolers (n=40)	Effect Size (Estimate)	*P* value
Sedation onset time (s)	38.5 (30.0–44.5)	38.0 (33.25–45.0)	0.001	0.343 †
Operation time (min)	11.5 (10.0–15.0)	15.0 (10.0–25.0)	0.021	0.110 †
Anesthesia time (min)	20.5 (16.3–28.8)	23.5 (18.0–33.5)	0.008	0.223 †
Wake-up time (min)	17.5 (15.0–20.5)	16.0 (13.0–20.5)	0.391	< 0.001 †
Adverse events, *n* (%)				
Hypotension	0 (0.0)	1 (2.5)	0.130, (0.112–0.260)	1.000 ‡
Bradycardia	0 (0.0)	0 (0.0)	0.352, (0.211–0.479)	< 0.001 ‡

Number (%)

[a] $P < 0.001$ versus preschoolers, calculated by Mann-Whitney *U* test with Bonferroni correction

[b] $P < 0.001$ versus schoolers, calculated by Mann-Whitney *U* test with Bonferroni correction

[c] $P = 0.036$ versus preschoolers and schoolers, calculated by Fisher's exact test with Bonferroni correction

† Kruskal-Wallis test, effect size reported as ϵ^2

‡ Fisher's exact test, effect size reported as Cramér's V with 95% CI