Randomized Clinical Trial

Dose Equivalence of Remimazolam and Propofol for Loss of Consciousness in Pediatric Patients: A Randomized Clinical Trial

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Background: Remimazolam and propofol can be used interchangeably for general anesthesia. However, no dosing recommendations exist for the intravenous bolus administration of remimazolam during general anesthesia induction in pediatric patients. Determining the appropriate dose for anesthesia induction in pediatric patients is crucial for safe and effective surgical procedures.

Objectives: The study aimed to determine the median effective dose (ED_{50}) for loss of consciousness (LOC) with remimazolam and propofol in pediatric patients and establish the dose equivalence between these anesthetics.

Study Design: A prospective, randomized, single-center trial.

Setting: A tertiary pediatric hospital in China from January 2023 to July 2023.

Methods: Pediatric patients aged 3 to 15 years, undergoing elective surgery under general anesthesia, were included. Patients were randomized to receive either remimazolam (in doses of 0.1, 0.15, 0.2, 0.25, and 0.3 mg/kg^{-1}) or propofol (in doses of 0.75, 1.0, 1.25, and 1.5 mg/kg^{-1}) via intravenous bolus. The primary measure consisted of determining the ED_{50} for LOC with remimazolam, and the secondary measure consisted of establishing the dose equivalence between remimazolam and propofol.

Results: The calculated ED50 for remimazolam was 0.19 mg/kg^{-1} (95% CI: 0.10–0.35), and that for propofol was 1.11 mg/kg^{-1} (95% CI: 0.53–2.15). This finding indicates that remimazolam is approximately 5.8 times more potent than propofol.

Limitations: In this study, the anesthesiologist could not be blinded to the different appearances of remimazolam and propofol, and the LOC assessment method may have introduced bias. Furthermore, the recommended dose for remimazolam induction was not tested directly within this trial, suggesting a need for further research.

Conclusions: Remimazolam demonstrates significantly higher sedative efficacy for pediatric patients than does propofol. An induction dose of 0.34 mg/kg^{-1} remimazolam could be recommended for general anesthesia induction, considering the safety and effectiveness of a 2 mg/kg^{-1} dose of propofol.

Key words: Remimazolam, propofol, pediatric anesthesia, loss of consciousness (LOC), median effective dose (ED_{50}), dose equivalence, intravenous bolus administration

Trial Registration: Registered at www.chictr.org.cn (ChiCTR 2200067112).

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Remimazolam is a novel ultrashort-acting benzodiazepine that is structurally similar to midazolam, has an added ester linkage, and acts on the benzodiazepine binding site of the gamma-aminobutyric acid receptor to yield a sedative effect (1,2). This benzodiazepine is metabolized by nonspecific tissue esterase enzymes; furthermore, its major metabolites have very low pharmacological activity. The advantages of remimazolam, including rapid onset of action, short recovery time, stable hemodynamics, and the availability of reversal agents, make it suitable for general anesthesia management (3).

Despite its association with significant injection pain and dose-related cardiorespiratory depression, propofol has become the gold standard for both the induction and maintenance of intravenous anesthesia, as well as for procedural sedation. Doi et al (4) compared the use of remimazolam (6 mg/kg^{-1} h^{-1} and 12 mg/kg^{-1} h^{-1} for induction and one mg/kg^{-1}/h^{-1} for maintenance) with that of propofol (2.0–2.5 mg/kg^{-1}for induction and 4–10 mg/kg^{-1}/h^{-1} for maintenance) throughout the entire duration of the sets of surgical procedures. Both techniques provided suitable anesthetic conditions for surgery, and no significant difference in the overall incidence of adverse reactions was observed between the groups of patients. Accordingly, remimazolam and propofol can be used interchangeably for general anesthesia. To the best of our knowledge, no dosing recommendations exist for achieving loss of consciousness (LOC) in pediatric patients through the intravenous bolus administration of remimazolam during general anesthesia induction. Additionally, the equivalent dose between remimazolam and propofol remains unclear. Because clinical options have expanded beyond propofol, the clinical use of remimazolam has recently increased. However, comprehensive pharmacodynamic analyses to guide this increased usage on pediatric patients are lacking. Our aims were twofold: to determine the median effective dose (ED_{50}) required for inducing LOC in pediatric patients through the intravenous bolus administration of remimazolam and to determine the equivalent dose between remimazolam and propofol.

Methods

Ethics

Ethical approval for this study (SCMCIRB-K2022151-1) was provided by the institutional review board of a pediatric hospital in China. Before recruitment began, the trial was registered at the Chinese Clinical Trial Registry Web site (ChiCTR 2200067112). Written informed consent was obtained from the patients' parents or legal guardians before any protocol-specific procedures were conducted.

Patient Population

We conducted a patient- and observer-blind, parallel, randomized controlled trial in the anesthesia department of a pediatric hospital in China. We enrolled pediatric patients who were between the ages of 3 to 15 years, had the physical status of I or II according to the American Society of Anesthesiologists' classification system, and were scheduled for elective surgery under general anesthesia between January 2023 and July 2023. The exclusion criteria were as follows: oral sedation (premedication) before securing intravenous access, a body mass index (BMI) of > 30 kg m^{-2}, significant hepatic or renal disease, current upper respiratory infections or other respiratory symptoms, and any contraindications to the study medications.

Randomization and Blinding

The children were randomly assigned into 2 groups: the remimazolam group (group R) and the propofol group (group P). Group R was further divided into 5 subgroups: R 0.1, R 0.15, R 0.2, R 0.25, and R 0.3; similarly, group P was divided into 4 subgroups: P 0.75, P 1.0, P 1.25, and P 1.5. Each subgroup comprised 10 patients. The dosages of the drugs and the sample size for each subgroup were determined based on preliminary experiments. A computer-generated random sequence with a block size of 9 was used to randomly assign each pediatric patient to one of 9 subgroups in a 1:1:1:1:1:1:1:1:1 ratio. The information regarding the assigned group was sealed in an envelope, which was not opened until the patient entered the operating room. The study drugs were prepared and administered by one anesthetist who was aware of the group allocation, with another assistant reexamining the doses. A third trained anesthesiologist, who was blinded to the group allocation, evaluated the patients' reactions and collected the data.

Protocol for Anesthesia

During the preoperative visit, pediatric patients and their parents were verbally informed about the operating room's environment and the anesthesia procedures. A topical numbing cream was applied to each patient's skin, and the intravenous cannula was inserted in the ward. Each patient was escorted by a parent to our pre-

operative holding area specifically designed for children, which had colorful pictures on the walls and available toys. All patients' heart rates, oxyhemoglobin saturation, noninvasive blood pressure, and bispectral index (BIS) values were monitored using a Philips HP Viridia 24/26 M1205A (Agilent). The baseline hemodynamic profile was recorded after allowing the patient to rest for 5 minutes in the comforting presence of their parents. Prior to the induction of anesthesia, each patient was asked to breathe spontaneously with 100% oxygen for preoxygenation. Subsequently, patients in the subgroups R 0.1, R 0.15, R 0.2, R 0.25, and R 0.3 received intravenous boluses of remimazolam from Hengrui Pharmaceutical Co., Ltd., at doses of 0.1 mg/kg^{-1}, 0.15 mg/kg^{-1}, 0.2 mg/kg^{-1}, 0.25 mg/kg^{-1}, and 0.3 mg/kg^{-1}, respectively. Similarly, patients in the subgroups P 0.75, P 1.0, P 1.25, and P 1.5 were administered IV propofol from Fresenius Kabi China Co., Ltd., at respective doses of 0.75 mg/kg^{-1}, 1.0 mg/kg^{-1}, 1.25 mg/kg^{-1}, and 1.5 mg/kg^{-1}. Each assigned dose of remimazolam or propofol was administered over 20 seconds, in accordance with the study protocol. LOC, respiratory depression (RD), and hemodynamic variables were assessed within 5 minutes after the completion of the anesthetic injection. LOC was defined as the absence of a response after the mild shaking of the shoulder, equivalent to a score of ≤ 1 point on the Modified Observer's Assessment of Alertness/Sedation Scale. RD was defined as the discontinuation of spontaneous breathing by the patient and therefore the warranting of assisted ventilation. We recorded the incidences of LOC and RD. The LOC assessment was performed at intervals of 10 seconds, while RD was measured continuously starting from the end of the anesthetic injection. Hemodynamic variables were continuously monitored for 5 minutes and recorded at regular intervals of 30 seconds.

After the study period of 5 minutes, deeper anesthesia was induced through inhalation of 5% sevoflurane in oxygen until the BIS value was ≤ 50 for 5 seconds. After LOC was reconfirmed, 2 $\mu g/kg^{-1}$ of fentanyl and 0.6 mg/kg^{-1} of rocuronium were administered intravenously to facilitate tracheal intubation. Starting from one minute after intubation, anesthesia was maintained through the inhalation of 3% sevoflurane in oxygen, the amount of which was adjusted to maintain adequate intraoperative anesthesia. Cardiorespiratory complications and other perioperative adverse events were also recorded.

Outcome Measures

The primary outcome was to establish the ED50 for achieving LOC in pediatric patients through the intravenous bolus administration of remimazolam. The secondary outcome involved determining the equivalent dosing ratio between remimazolam and propofol.

LOC Analysis

The variable of LOC after drug administration was coded as 0 (failure to achieve LOC) or 1 (successful LOC achievement). A logistic regression model was used to determine the ED_{50} and estimate the impact of covariates on LOC.

The statistical significance of a covariate was examined using the objective function value (OFV). In the forward screening process, after the addition of a single parameter to the model, an OFV improvement of > 3.84 was considered statistically significant (χ^2 distribution; df = 1; $P \leq 0.05$). For the backward deletion process, after the deletion of a single parameter from the model, an OFV improvement of > 6.63 was considered statistically significant (χ^2 distribution; df = 1; $P \leq 0.01$). Continuous covariates were introduced into the model as the participants' median value. Categorical covariates were coded as 0 and 1 (e.g., regarding gender: 1 for men and 0 for women).

$Pi = e^{Logit_i})/(1+e^{Logit_i})$ - Equation 1

$Logit_i = Intercept_i + Slope_i * Dose_j + \eta_i$ - Equation 2

In Equation 1, Pi represents the probability of LOC equal to 1 for the ith individual. In Equation 2, Intercepti is the intercept parameter value for the individual subject i, $Slope_i$ is the slope parameter value for the individual subject i, $Dose_j$ is the observation dose, and η_i is the interindividual variability, assumed to be normally distributed with a mean of 0 and a variance of σ^2.

The prediction bias and precision of our final models were evaluated using the visual predictive check.

Statistical Analyses

Outcome data of the intention-to-treat population were analyzed. The Shapiro-Wilk test was used to assess the normality of the data distribution. Normally distributed variables and categorical variables are presented as means ± SD and numbers (percentages), respectively. One-way analysis of variance (ANOVA) and the Dunnett T3 method were used for normally and nonnormally distributed continuous variables, respectively, while categorical data were compared using the chi-square test. Repeated-measures ANOVA was used for intergroup comparisons of continuous variables. The Bonferroni adjustment controlled for type I errors

in multiple testing. Statistical analyses were performed using SPSS® 28.0 for Windows (IBM Corporation). Statistical significance was set at $P < 0.05$.

Results

Among the 92 patients who were screened, we excluded 2 pediatric patients whose parents withheld consent. Finally, 90 patients were enrolled. The mean values of patients' age, weight, and height were 7.8 ± 3.4 years, 31.8 ± 15.8 kg, and 129.4 ± 23.1 cm, respectively. Fig. 1 presents the study flowchart and group assignment. There were no significant intergroup differences in the demographic characteristics (Table 1). The number of patients who achieved LOC in subgroups R 0.1, R 0.15, R 0.2, R 0.25, and R 0.3 were 0, 4, 7, 7, and 10, respectively; in subgroups P 0.75, P 1.0, P 1.25, and P 1.5, the patients who reached LOC numbered 0, 5, 8, and 10, respectively. There were 4 cases of RD, all occurring in the group of patients who received 1.5 mg/kg^{-1} of propofol. None of the patients experienced other complications, and all remained stable throughout the study.

Fig. 2 shows the relationship between the dose administered and the probability of LOC. When the probability of LOC was equal to 0.5, the ED50 of remimazolam and propofol for LOC was 0.19 mg/kg^{-1} (95% confidence interval [CI]: 0.10–0.35) and 1.11 mg/kg^{-1} (95% CI: 0.53–2.15), respectively. None of the assessed covariates, including age, gender, weight, and BMI, affected the ED_{50}. Table 2 shows the principal model parameters for the logistic regression model of LOC.

Model Evaluation

The prediction utility of the LOC model was evaluated using the visual predictive check. The results showed that the 95% CI predicted by the model was generally consistent with the measured value, indicating good predictive value (Figs. 3,4).

Discussion

This study investigated the ED_{50} of a single bolus dose of remimazolam for LOC in pediatric patients aged 3-15 years, as well as the equivalent dose between remimazolam and propofol.

Although the BIS value demonstrates good correlation with sedation levels that occur during anesthesia, including those observed in patients under the influence of inhalation anesthetics and propofol (5), studies have shown that the BIS value witnessed during remimazolam-induced anesthesia tends to be higher than the BIS value seen during propofol-induced anesthesia (6). Currently, there is no established gold standard for assessing the appropriate sedation levels in patients who have taken remimazolam. The MOAA/S scale is the most

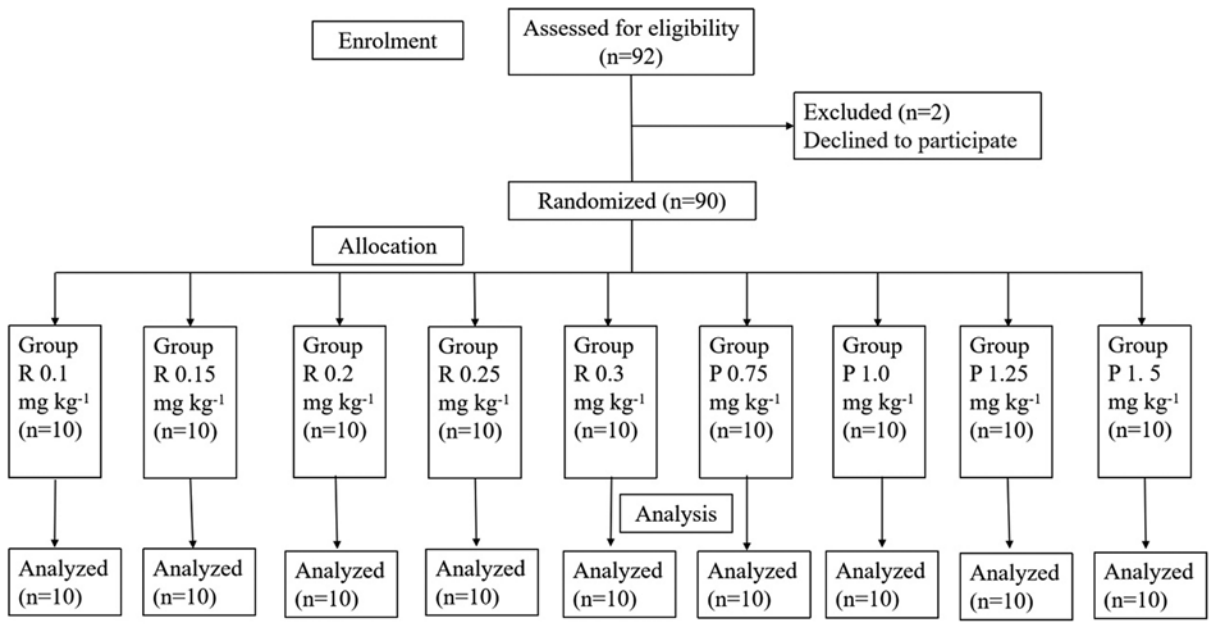

Fig. 1. *Flow diagram of included patients.*

Table 1. *Patient demographics (n = 10 per group).*

Group	Remimazolam (mg/kg^{-1})					Propofol (mg/kg^{-1})			
	R 0.1	R 0.15	R 0.2	R 0.25	R 0.3	P 0.75	P 1	P 1.25	P 1.5
Age (years)	7.65 ± 4.19	6.81 ± 3.51	7.64 ± 4.81	8.06 ± 3.50	7.76 ± 2.83	7.99 ± 2.41	8.03 ± 3.89	8.77 ± 2.61	7.20 ± 3.67
Gender (M/F)	7/3	8/2	9/1	8/2	7/3	9/1	8/2	9/1	8/2
Weight (kg)	36.47 ± 23.39	26.33 ± 13.52	34.79 ± 25.46	28.68 ± 10.27	32.07 ± 14.66	31.30 ± 13.00	31.93 ± 14.56	36.06 ± 13.70	28.63 ± 10.26
Height (cm)	129.10 ± 31.01	120.90 ± 21.51	129.10 ± 31.02	130.50 ± 23.10	131.30 ± 19.13	129.40 ± 17.18	130.50 ± 28.07	136.70 ± 15.68	127.20 ± 22.14
BMI (kg m^{-1})	19.17 ± 4.79	16.90 ± 3.76	18.52 ± 4.67	16.43 ± 2.12	17.78 ± 2.80	17.76 ± 3.53	17.70 ± 1.40	18.56 ± 3.79	17.29 ± 1.90
ASA physical status (II/III)	4/6	5/5	3/7	7/3	4/6	6/4	7/3	8/2	6/4

Data are presented as the mean ± SD, except for gender and ASA physical status, which are given as absolute numbers.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; F, female; M, male.

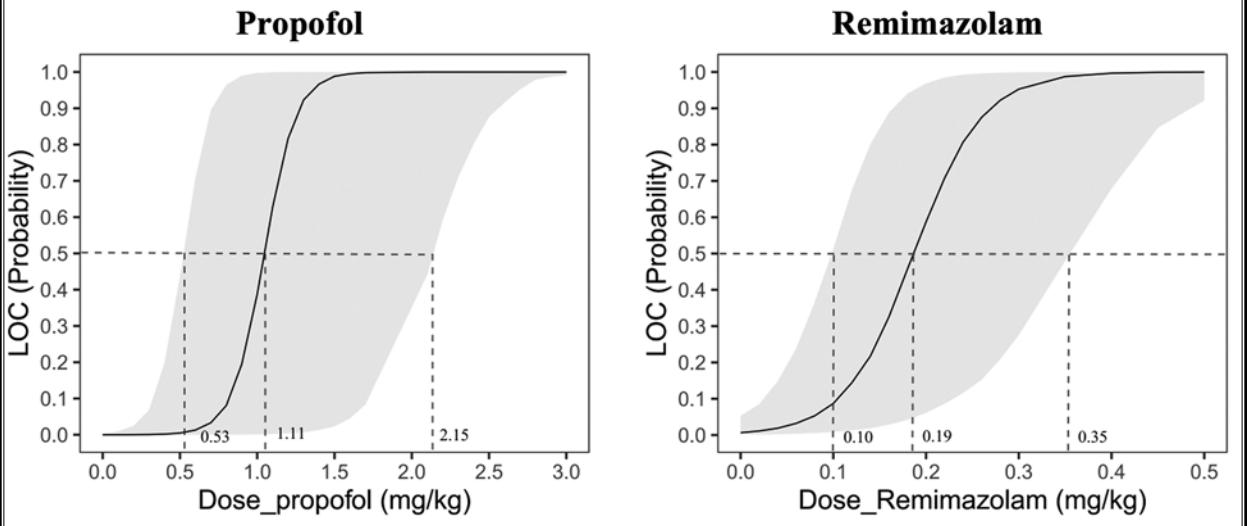

Fig. 2. *Probability relationship curve between dose and loss of consciousness. The black line represents the typical value of the model simulation, with the blue shaded area representing the 95% confidence interval of the typical value simulated by the model. The 3 dose levels represent the dose interval when the probability of loss of consciousness is equal to 0.5.*

widely used and reliable indicator of anesthesia depth in clinical practice, and this rubric could serve as a supportive measure for assessing patient sedation levels during anesthesia induced by remimazolam (7).

The ED_{50} of remimazolam for LOC was 0.19 mg/kg^{-1} (95% CI: 0.10–0.35), regardless of age, gender, weight, or BMI. Most previous studies on remimazolam applied continuous infusion for anesthesia induction (8,9). Previous studies have observed differences in fitted pharmacokinetic parameters according to the drug-delivery methods (10,11). Specifically, a single bolus injection has a higher peak concentration than does continuous infusion. In practice, intravenous anesthesia induction is usually performed using a single bolus dose to achieve high drug concentrations rapidly and thus induce LOC quickly. It is necessary to explore the ED_{50} of a single bolus dose of

Table 2. *Parameters for the logistic regression model of loss of consciousness.*

Group	Propofol		Remimazolam	
	Estimate	RSE%	Estimate	RSE%
Intercept	-10.2	22.7	-5.03	21.7
Slope	9.73	23.8	26.9	21.2

Abbreviations: RSE, residual standard error

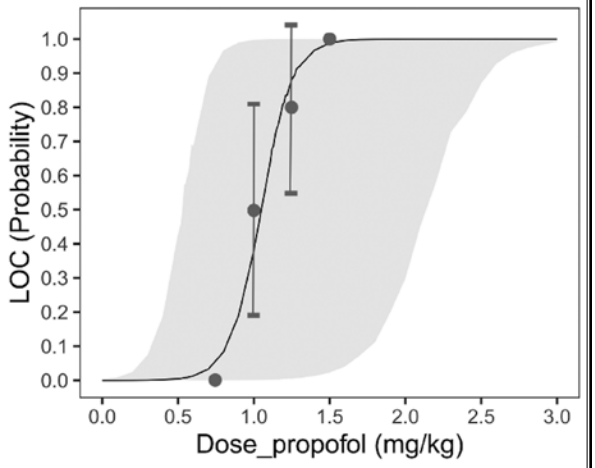

Fig. 3. *Model validation of propofol. The solid points represent the observed mean P-value of loss of consciousness, and the error bar represents the 95% confidence interval of the mean value. The black line represents the typical value of the model simulation, with the blue shaded area representing the 95% confidence interval of the typical value simulated by the model.*

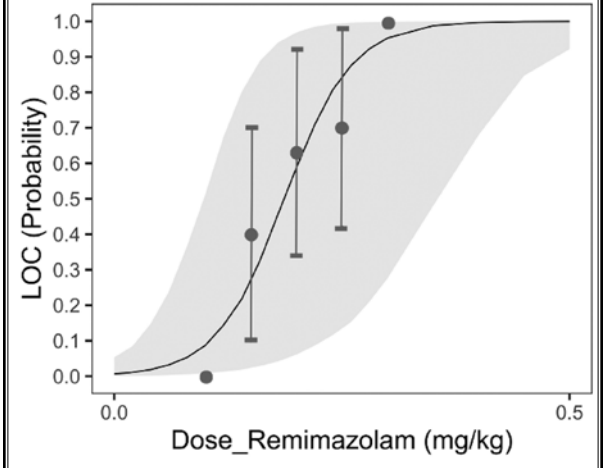

Fig. 4. *Model validation of remimazolam. The solid points represent the observed mean P-value of loss of consciousness, and the error bar represents the 95% confidence interval of the mean value. The black line represents the typical value of the model simulation, with the blue shaded area representing the 95% confidence interval of the typical value simulated by the model.*

remimazolam from a clinical perspective. Chae et al (12) reported that older patients required a lower ED_{50} to achieve LOC than did younger patients. In contrast, our findings indicate that the ED_{50} is not influenced by age. This discrepancy could be attributable to differences in the ages of the patients enrolled in the studies. Specifically, Chae et al recruited patients aged 21-88 years, while we recruited pediatric patients aged 3-15 years. To the best of our knowledge, this is the first study to report the ED_{50} of an intravenous bolus of remimazolam for LOC in pediatric patients. In a difference from the previous reports concerning adults (7,13), we observed an increase in the remimazolam dose required for pediatric patients to reach LOC. To some extent, the peak concentration of remimazolam depends on its central distribution volume and systemic clearance. However, systemic clearance is not a relevant factor when remimazolam is administered as a bolus for fast LOC achievement. A previous study revealed that, after a bolus dose administration, children exhibited a larger central compartment volume (14) than did adult patients. This difference is attributed to children's relatively greater extracellular and total body water space compared to adults (7,15).

Remimazolam is considered an effective alternative to propofol for intravenous anesthesia and sedation, since remimazolam produces comparatively less cardiac and respiratory depression and a negligible accumulative effect over time, given its elimination by tissue esterases and the reversal of its effect by the benzodiazepine antagonist flumazenil (16). However, there remains no clinically recommended equivalent dose and medication experience for pediatric patients. Moreover, the lack of an established equivalent dose between remimazolam and propofol implies that their pharmacologic properties cannot be quantitatively compared. Remimazolam and propofol had a respective ED_{50} of 0.19 and 1.11 mg/kg^{-1} for LOC. The sedative efficacy of remimazolam is 5.8 times (ED_{50}-remimazolam/ED_{50}-propofol) that of propofol. Since an anesthesia induction dose of 2 mg/kg^{-1} propofol has generally been considered safe and effective (17,18), it may be assumed that 0.34 mg/kg^{-1} remimazolam may yield similar clinical outcomes. This assumed dose is consistent with our finding that the ED_{95} of remimazolam is 0.35 mg/kg^{-1}. Dai et al (19) have reported that the efficacy of a single dose of ≥ 0.3 mg kg^{-1} remimazolam is similar to that of 2 mg kg^{-1} propofol during anesthesia induction, which is consistent with the results of our study.

Limitations

This study has some limitations. First, we could

not double-blind the anesthesiologist, given the differences in color between remimazolam and propofol. Although an evaluator blinded to group allocation performed intergroup analysis to avoid bias, doing so could not have effectively eliminated theoretical bias. Second, we defined LOC as the absence of a response to mild shaking. Although the same single-blinded evaluator performed mild shaking to decrease bias, a more standardized and reproducible stimulus may have allowed a more accurate assessment of LOC. Third, based on the equivalent dose estimates, 0.34 mg/kg^{-1}remimazolam was recommended for the induction of general anesthesia in pediatric patients. This concentration was not used in our study. Therefore, more clinical research and follow-up studies are warranted.

Conclusions

In conclusion, our findings indicated that the ED_{50} of remimazolam for LOC in pediatric patients was 0.19 mg/kg^{-1}; additionally, the sedative efficacy of remimazolam was 5.8 times that of propofol. Since inducing anesthesia with a dose of 2 mg/kg^{-1} of propofol is safe and effective, 0.34 mg/kg^{-1} of remimazolam may be appropriate for the induction of general anesthesia in pediatric patients.

Author Contributions

Yang Shen helped with substantial contributions to the acquisition, analysis, and interpretation of data for the work as well as its drafting.

Ying Sun helped with substantial contributions to the design of the study, the acquisition of data for the work, and revising the paper critically for important intellectual content.

Yan-Ting Wang helped with substantial contributions to the acquisition, analysis, and interpretation of data for the work.

Zhe-Zhe Peng helped with substantial contributions to the acquisition, analysis, and interpretation of data for the work.

Jie Bai helped with substantial contributions to the acquisition, analysis, and interpretation of data for the work.

Ji-Jian Zheng helped with substantial contributions to the acquisition, analysis, and interpretation of data for the work.

Ma-Zhong Zhang helped with substantial contributions to the conception and design of the study, the analysis and interpretation of data for the work, and making critical revisions for important intellectual content.

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