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CLINICAL TRIAL REPORT

# ED90 of Remimazolam for Moderate Sedation in Children Undergoing Neurosurgery

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**Background:** Preoperative sedation is critical to alleviate anxiety in children undergoing neurosurgery, but the role of remimazolam is still uncertain such as its unestablished dosing and safety. This study was aimed to determine the 90% effective dose (ED90) of remimazolam for moderate sedation in this pediatric population.

**Methods:** This dose-finding study enrolled children aged 3 months to 6 years scheduled for neurosurgery. The up-and-down method (k-in-a-row, k= 6) was employed to investigate the ED90 of remimazolam for moderate sedation. According to the k-in-a-row rule, one patient received a predefined dose of remimazolam and the dosing assignment of the next patient depended on whether the former patient reached moderate sedation or not. Moderate sedation was assessed using the modified Observer's Assessment of Alertness/Sedation (MOAA/S). Remimazolam doses ranged from 0.05mg/kg to 0.35mg/kg with a step gradient of 0.05mg/kg. The ED90 and 95% confidence interval (CI) were calculated by centered isotonic regression. Secondary outcomes included drug-related adverse events, the incidence of emergence delirium (ED), and changes in brain network connectivity which were monitored by functional near-infrared spectroscopy (fNIRS).

**Results:** Forty-eight children were enrolled with a median age of 20.5 (9.0, 35.0) months. The ED90 of remimazolam for moderate sedation was 0.28 (95% CI 0.24–0.42) mg/kg. The incidence of drug-related adverse events was about 12.5%, including respiratory depression and hiccup. The incidence of ED was 62.2%. fNIRS showed increased connectivity in right frontal lobe-right occipital lobe, right frontal lobe-left occipital lobe, and right frontal lobe-left parietal lobe (all P values < 0.05 after correction by false discovery rate).

**Conclusion:** This study reported the ED90 of remimazolam for moderate sedation in neurosurgical children. These results provided important information for the use of remimazolam in children with neurologic disease.

**Keywords:** remimazolam, pediatrics, neurosurgery, moderate sedation, brain network connectivity

## Introduction

Preoperative anxiety is a common psychological behavior in children undergoing surgery, which is manifested by restlessness, crying, and attempts to escape from medical staff. Children undergoing neurosurgery are prone to suffer anxiety due to the influence of neurological diseases. For example, hydrocephalus accounts for more than 70% of pediatric neurosurgeries, and children with hydrocephalus typically require multiple surgical interventions and experience repeated exposure to anesthesia.[1] The incidence of anxiety in these patients is about 40%.[2] Anxiety may increase the risks of emergence delirium (ED) and postoperative negative behaviors (ie, nightmares, separation anxiety, and aggressive behaviors).[3]

Sedatives such as propofol, dexmedetomidine, and midazolam are commonly used as premedication to alleviate preoperative anxiety. Although their anxiolytic effects have been well-validated, each of them has clinical limitations. For

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instance, propofol is associated with injection pain and an increased risk of respiratory depression; dexmedetomidine has a slow onset of action and may cause bradycardia; midazolam, a classic benzodiazepine, may lead to delayed emergence.[4–6]

Remimazolam is an ultra-short-acting benzodiazepine with an elimination half-life of only three to five minutes. It is widely used for procedural sedation in adults with the advantages of rapid onset and less disturbance to respiration and hemodynamics.[7] Recent studies showed that remimazolam anesthesia had the advantages of rapid recovery and lower occurrence of ED in non-neurosurgical pediatric patients.[8] Considering that neurosurgical children might be more intolerant to general anesthetics, we proposed that remimazolam might benefit these children because of its short-acting duration and less disturbance to respiration and hemodynamics.[9]

The primary objective of this study was to investigate the ED90 of remimazolam for preanesthetic moderate sedation in children aged 3 months to 6 years undergoing elective neurosurgery.

## Materials and Methods

This study was a prospective dose-finding study. Ethical approvals were obtained from the Biomedical Ethics Committee of Peking University First Hospital (No. 2022–529) and complied with the Declaration of Helsinki. Written informed consent was obtained from the legal representatives of all children. The trial was registered prior to patient enrollment at the Chinese Clinical Trial Registry (No. ChiCTR200067134, Principal investigator: Dong-Liang Mu, date of registration: December 27, 2022, https://www.chictr.org.cn/showproj.html?proj=187614). Enrollment of the first patient took place on March 7, 2023.

### Participants

This study enrolled children aged three months to six years who were scheduled for elective neurosurgery under general anesthesia. Exclusion criteria were as follows: (1) allergy to benzodiazepines; (2) use of benzodiazepines within recent one week; (3) use of other sedatives such as propofol and chloral hydrate within 24 hours prior to surgery; (4) took part in other studies within recent one month; and (5) the children or their legal representatives refused to participate.

### Primary Outcome

The primary outcome was the ED90 of remimazolam for pre-anesthesia moderate sedation. The modified Observer's Assessment of Alertness/Sedation (MOAA/S) is a five-score scale with 1 for loss of consciousness and 5 for being completely awake.[10] Moderate sedation was defined as MOAA/S score at 3 (delayed response to loud or repeated sound of name). The researchers assessed the sedation depth every three seconds after administration of the study drug. A positive sedation case was established if the MOAA/S score reached 3 or lower within one minute.

To keep the quality of sound stimulation, we used the same smartphone to record the sound of the parents calling the children's nicknames. A smartphone decibel meter was used to control the sound intensity: 40 decibels for normal sound and 70 decibels for loud sound.[11] The recording sound was played at a distance of 10 cm to children's ears.

The ED90 and its 95% confidence interval (CI) were calculated using centered isotonic regression, which models dose–response relationships to estimate the threshold dose achieving the desired level of response in 90% of patients.

### Secondary Outcomes

The secondary outcomes included: (1) drug-related adverse events, (2) the incidence of ED, and (3) the effect of remimazolam on brain network connectivity.

Drug-related adverse events were observed from administration of the study drug to anesthesia induction. Injection pain was categorized into four levels: level 1 (no pain, no response to injection); level 2 (mild pain, mild language, facial, or motor reactions to injection); level 3 (moderate pain, obvious language, facial, or motor reactions to injection); and level 4 (severe pain, subjective complaints of pain and retracting the arm).[12] Hypotension and bradycardia were defined as a decrease in systolic blood pressure or heart rate ≥20% from baseline with medical treatment (ie, vasoactive drugs), respectively. Respiratory depression was defined as $SpO_2$< 90% when breathing air and requiring interventions such as oxygen supplementation, jaw thrust, or manual ventilation. Hiccup was defined as the occurrence of diaphragmatic spasm following the administration of remimazolam. Delayed recovery was defined as emergence time≥ 30 minutes.

The Cornell Assessment of Pediatric Delirium (CAPD) was used to assess ED within 30 minutes after extubation. The sensitivity and specificity of CAPD were 92% and 86.5% in Chinese children, respectively.[13]

The functional near-infrared spectroscopy (fNIRS) system, a non-invasive monitoring system with high temporal resolution, was employed to monitor brain network connectivity for 3 minutes one day before surgery and after achieving moderate sedation.[14] The 46-channel fNIRS system (NirSmart-2416, Huichuang Ltd., China) consists of 24 light-emitting sources (two near-infrared wavelengths of 760nm and 850nm) and 16 detectors.[15] This device supported automatic adjustment of source power and detector gain to optimize signal quality. The average signal-to-noise ratio of channels was 22.2 ± 12.1dB. Data at each channel were sampled at 10Hz and were recorded by NIRScan software in real-time.

In terms of the Montreal Neurological Institute coordinates, this study used a standard head form to determine the center points of each light source and detector. The channels were assigned to referring anatomical positions based on the automatic anatomical labeling (Figure S1). All 46 channels were divided into 8 regions of interest (ROIs): right frontal lobe (RFC), left frontal lobe (LFC), right temporal lobe (RTL), left temporal lobe (LTL), right parietal lobe (RPL), left parietal lobe (LPL), right occipital lobe (ROL), left occipital lobe (LOL) (Table S1).

## Dose Regimen of Remimazolam and Rescue Sedation

The dose regimen of remimazolam was set from 0.05mg/kg to 0.35mg/kg with a step gradient of 0.05mg/kg. Considering the lack of evidence regarding its use for pediatric sedation, the dose regimen of remimazolam was designed in relation to procedural sedation in adult patients (ie, 0.14–0.33 mg/kg).[7]

The k-in-a-row up-and-down method was used to investigate the ED90 of remimazolam for moderate sedation and k was set at 6.[16] According to the k-in-a-row method, one patient received a predefined dose of remimazolam and the next patient would be treated with the following dose assignments: (1) if the preceding patient did not achieve sedation, the next patient would receive an increased dose; (2) if the preceding patient achieved sedation, the next patient would receive the same dose; or (3) the next patient would receive a decreased dose after observing 6 consecutive sedation at the same dose.[16]

If a patient failed to achieve sedation within 1 minute after receiving the study drug, propofol 0.5–1mg/kg would be given for rescue sedation to maintain patient safety and integrity of the sedation process. This observation interval was selected based on our pilot study of 21 children.

## Blinding Method

A designated researcher prepared remimazolam into 3mL colorless liquid using identical syringes. This researcher was not involved in drug administration, sedation assessment, or follow-up procedures. An attending anesthesiologist took charge of drug administration, while another anesthesiologist was responsible for sedation assessment and postoperative follow-up. Both of them were blinded to the drug dose.

## Perioperative Management and Anesthesia

One day before the surgery, eligible patients were visited by the researchers. After obtaining written inform consent, baseline characteristics were collected such as demographic data and comorbidities. The parent's sound of calling children's nicknames were recorded. When children were quiet and breathed air, fNIRS was used to monitor brain network connectivity for three minutes.

On the day of surgery, the modified Yale preoperative anxiety scale (m-YPAS) was used to assess the severity of anxiety in the waiting area. m-YPAS $\geq$ 30 indicated preoperative anxiety.[17] Standard physiological measurements were applied to all participants including electrocardiogram, non-invasive blood pressure measurement, and peripheral arterial oxygen saturation. The study drug was administered under continuously monitoring to ensure safety. In patients who were successfully sedated by remimazolam, brain network connectivity was assessed by fNIRS for three minutes.

Anesthesia induction included propofol 2–4 mg/kg, sufentanil 0.1–0.2 μg/kg, and cis-atracurium 0.05–0.1 mg/kg. Anesthesia maintenance was achieved by continuous infusion of propofol 4–8 mg/kg/h and remifentanil 0.05–0.2 μg/kg/min. Cis-atracurium was intermittently given to maintain muscle relaxation. Anesthesia management was aimed to maintain the fluctuation of systolic blood pressure within 20% baseline reference, end-expiratory carbon dioxide at 35–45mmHg, and body temperature at 36–37°C.

## Sample Size Calculation

To determine the sample size, a pilot observation was conducted in 21 children with the dosage of remimazolam from 0.05mg/kg to 0.35mg/kg. To achieve moderate sedation, the standard deviation of the remimazolam dose was 0.14mg/kg and the standard error was 0.03mg/kg. According to Dixon and Massey's formula (n=2 $[SD/SEM]^2$) and a dropout rate of 10%, 49 patients were needed.[18]

## Statistical Analysis

The normality of continuous variables was assessed using histograms. Variables with normal distribution were presented as mean (standard deviation, SD) and compared using the independent samples *t*-test. Otherwise, continuous variables were presented as median (interquartile, IQR) and compared using the Mann–Whitney *U*-test. Categorical data were presented as number (percentage) and compared using the chi-square test or Fisher's exact test, as appropriate.

For primary outcome, the centered isotonic regression was used to determine the ED90 and 95% confidence interval (CI).[16] For sensitivity analysis, the dose and onset time to moderate sedation in different age were analyzed using Kruskal–Wallis *H*-test. For secondary outcomes, drug-related adverse events and ED were presented as number (percentage). Chi-square or Fisher's exact test was used for between-group comparison.

To analyze the fNIRS data at baseline and moderate sedation, the temporal derivative distribution repair method was used to correct head motion artifacts.[19] Subsequently, a bandpass filter with a range from 0.01 to 0.2Hz was applied to remove noise caused by physiological signals such as pulse and respiration. According to the modified Beer-Lambert law, the light intensity data were converted into relative changes of oxyhemoglobin and deoxyhemoglobin concentration.[20] The time series of hemoglobin concentrations in 8 ROIs were averaged. The inter-region correlation was calculated using Pearson correlation analysis. Then, Fisher's r-z transformation was applied to convert these correlation coefficients into z-scores for improving normality. Paired *t*-test was used to compare the changes of connectivity strengths between baseline and moderate sedation. False discovery rate (FDR) was used for multiple comparison correction.

Graph theory method was used to construct the brain network connectivity.[21,22] We calculated the correlation between all channels and obtained a connectivity matrix of 46 × 46, which was then transformed into a binary matrix based on a threshold (ie, a sparsity of 30%) to construct the brain connectivity network model. The following topological properties of global and local networks were calculated (Supplementary Material 1). The normalized clustering coefficient measured the likelihood of nodes being connected to each other, reflecting the processing efficiency of local brain regions. The shortest path length was defined as the average optimal path from one node to another in the network. Modularity was referred to the degree of nodes with dense internal connections and sparse external connections in a network. Global efficiency evaluated the overall transmission capacity of information flow in the network, calculated as the average of the reciprocal of the shortest path length between all node pairs. Local efficiency assessed the efficiency of information transmission near each node. The small-worldness was defined as the ratio of the clustering coefficient to the shortest path length. To compare with the small-worldness of real networks, 1000 random networks were constructed with the same number of nodes, edges, and degree distribution. Paired *t*-test was performed to compare the changes of connectivity strengths between baseline and moderate sedation for the above network parameters.

Data were analyzed by SPSS software (SPSS 26, IBM, Inc. Chicago, IL, USA) and the "cir" package in the open-source statistical programming language R (version 4.4.1, R Core Team). fNIRS data were analyzed by a simple mixed ANOVA in MATLAB (R2022b, The MathWorks, Inc., USA). The p value $< 0.05$ was considered as statistical significance if not specified.

# Results

## Participant

From March 7, 2023 to June 25, 2023, a total of 175 children were screened and 49 of them were eligible. One child's mother withdrew inform consent before surgery and this child did not receive study drug. Forty-eight subjects were finally included for analysis (Figure 1). The median age of these children was 20.5 (9.0, 35.0) months and the median body weight was 11.3 (8.1–13.2) kg. The preoperative m-YPAS scores were about 23.3 (23.3, 46.7), and 22 children (45.8%) were classified as preoperative anxiety. Other perioperative variables are shown in Table 1.

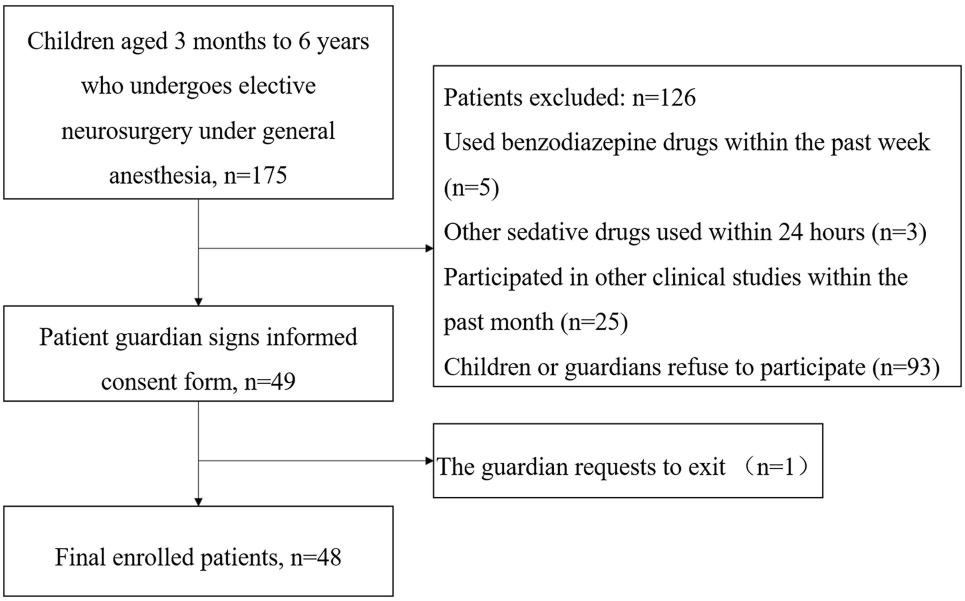


**Figure 1** Flow chart.

## Primary Outcome

The centered isotonic regression model showed that the ED90 of remimazolam for moderate sedation was 0.28 (95% CI 0.24–0.42) mg/kg. The success rate of remimazolam-induced moderate sedation was approximately 81.3% (39/48) (Figure 2). Nine patients received propofol for rescue sedation.

Among the 39 patients who achieved successful sedation with remimazolam, the median dose of remimazolam was 0.25 (0.25, 0.35) mg/kg. In the sensitivity analysis, no statistically significant difference was observed in the median

**Table 1** Baseline Variables

| Variables | Value (n=48) |
|---|---|
| Age (months) | 20.5 (9.0, 35.0) |
| Infants (3 months to 1 year) | 21 (43.8%) |
| Toddlers (1–3 years) | 17 (35.4%) |
| Preschoolers (3–6 years) | 10 (20.8%) |
| Height (cm) | 82.1 (15.0) |
| Weight (Kg) | 11.3 (8.1, 13.2) |
| Male | 30 (62.5%) |
| Premature | 20 (41.7%) |
| Comorbidities | |
| Cardiovascular system | 4 (8.3%) |
| Metabolic system | 1 (2.1%) |
| History of general anesthesia | 37 (77.1%) |
| 0 | 13 (27.1%) |
| 1 | 23 (47.9%) |
| ≥2 | 12 (25.0%) |
| Preoperative m-YPAS score | 23.3 (23.3, 46.7) |
| Preoperative anxiety (m-YPAS>30) | 22 (45.8%) |
| ASA class | |
| 1 | 46 (95.8%) |
| 2 | 2 (4.2%) |

(*Continued*)


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**Table 1** (Continued).

| **Variables** | **Value** (n=48) |
|---|---|
| Surgery type | |
| Shunt and external drainage surgery | 35 (72.9%) |
| Tumor resection | 9 (18.8%) |
| Epilepsy surgery | 3 (6.3%) |
| Cranial suture reconstruction | 1 (2.1%) |
| Operative time (min) | 63.0 (52.5, 141.3) |
| Anastasia time (min) | 173.5 (145.0, 253.0) |
| Postoperative in-hospital stay (days) | 10.5 (10.0, 17.0) |

**Notes**: Data were presented as mean (standard deviation), median (interquartile) or number (percentage). Cardiovascular system included 1 case of ventricular septal defect, 1 case of patent ductus arteriosus, and 2 cases of patent foramen ovale. 1 case of Metabolic system was Methylmalonic aciduria. The m-YPAS score ranges from 0 to 100 points, with higher scores indicating more severe anxiety levels. m-YPAS ≥ 30 indicated preoperative anxiety.
**Abbreviations**: m-YPAS, modified Yale preoperative anxiety scale; ASA, American Society of Anesthesiologists.

remimazolam dose across different age groups: 0.30 (0.25, 0.35) mg/kg for infants (3 months to 1 year, n=17), 0.25 (0.25, 0.35) mg/kg for toddlers (1–3 years, n=13), and 0.25 (0.23, 0.30) mg/kg for preschoolers (3–6 years, n=9) (Kruskal–Wallis *H*-test, P=0.611) (Table S2).

The time to onset of moderate sedation was 9.00 (6.00, 12.00) seconds, with no statistically significant differences observed across different age groups (Kruskal–Wallis *H*-test, P=0.155) (Table S3).

## Secondary Outcomes

The incidence of drug-related adverse events was about 12.5% (6/48), which included 5 cases of respiratory depression and 1 hiccup (Table 2). No patient experienced injection pain, bradycardia, hypotension, or delayed recovery. Additionally, all respiratory depression cases were mild and resolved after oxygen supplementation. The single case of hiccup was self-limiting within 5 minutes without clinical intervention. In this study, 62.2% (28/45) of the children experienced ED.

In 39 patients with remimazolam-induced moderate sedation, 30 patients of them completed fNIRS monitoring both at baseline and moderate sedation. In comparison with baseline, the changes in connectivity strengths between most ROIs

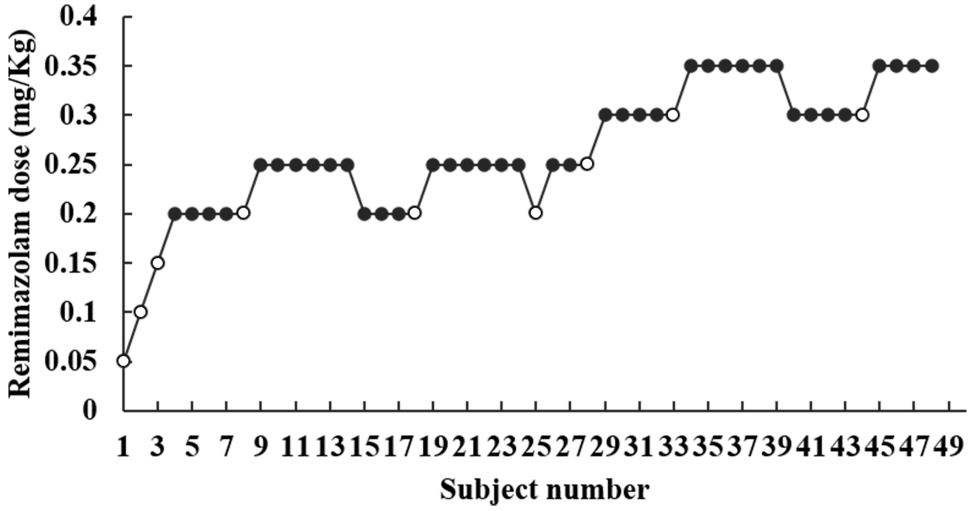


**Figure 2** The dose–response curve of remimazolam for sedation. Solid dots indicated successful sedation and circles indicated failed sedation.

**Table 2** Drug-Related Adverse Events

| Adverse Events | All Subjects (n=48) | ≤0.2mg/Kg (n=13) | 0.25mg/Kg (n=15) | 0.3mg/Kg (n=10) | 0.35mg/Kg (n=10) |
|---|---|---|---|---|---|
| Bradycardia | 0 | 0 | 0 | 0 | 0 |
| Hypotension | 0 | 0 | 0 | 0 | 0 |
| Injection pain | 0 | 0 | 0 | 0 | 0 |
| Respiratory depression | 5 (10.4%) | 0 | 4 (26.7%) | 1 (10.0%) | 0 |
| Hiccup | 1 (2.1%) | 0 | 1 (6.7%) | 0 | 0 |
| Delayed recovery | 0 | 0 | 0 | 0 | 0 |

**Notes**: Bradycardia was defined as a decrease in heart rate ≥ 20% of the baseline reference and required treatment (ie, vasoactive drugs). Hypotension was defined as a decrease in systolic blood pressure ≥ 20% of the baseline reference and required treatment (ie, vasoactive drugs). Injection pain was defined as mild or obvious language, facial, and motor reactions to injection, or with patient complaining of pain and retracting the arm. Respiratory depression was defined as $SpO_2$< 90% and required interventions such as oxygen supplementation, jaw thrust, or manual ventilation. Hiccup was defined as the occurrence of diaphragm spasm following the administration of remimazolam. Delayed recovery was defined as emergence time ≥ 30 minutes.

had no statistical significance, except increased connectivity strengths in RFC-ROL (P=0.0015), RFC-LOL (P=0.0007), and RFC-LPL (P=0.0029) (all P values < 0.05 after FDR correction) (Figures 3 and S2).

No statistical significance was observed in the topological properties of the brain network between baseline and moderate sedation, including normalized clustering coefficient, global efficiency, local efficiency, modularity, and small-worldness (all P values > 0.05) (Figure 4).

# Discussion

## ED90 of Remimazolam for Moderate Sedation in Neurosurgical Children

This study found that the ED90 of remimazolam for moderate sedation was 0.28 (95% CI 0.24–0.42) mg/kg in neurosurgical children aged 3 months to 6 years. The fNIRS monitoring showed that remimazolam-induced moderate sedation had little effect on connectivity strengths and topological properties of brain network, except increased connectivity strengths in RFC-ROL, RFC-LOL, and RFC-LPL.

The incidence of preoperative anxiety was about 45.8% in this study, which was aligned with the previously reported incidence.[23] The severity of pediatric anxiety was assessed using m-YPAS. This scale has been widely used and validated with sensitivity at 86% and specificity at 74% in surgical children.[24]

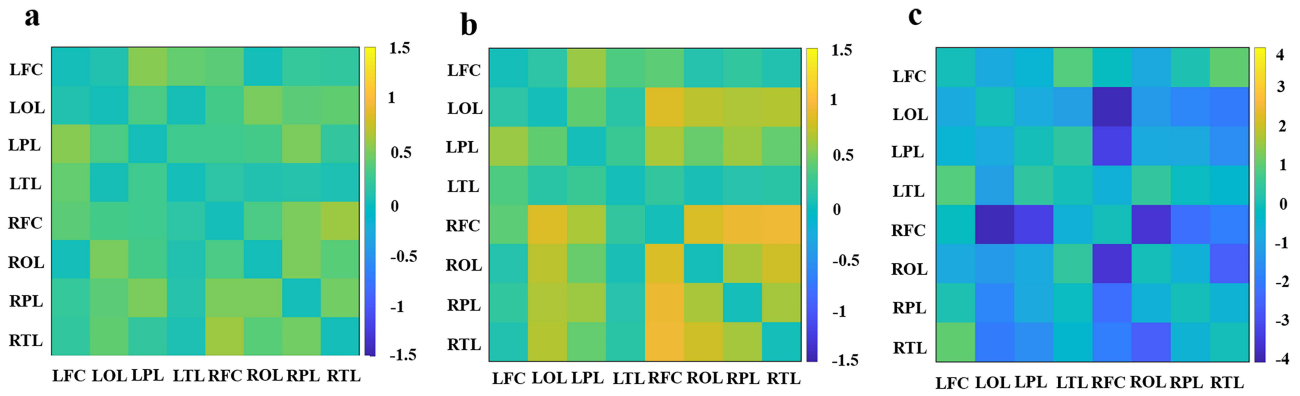


**Figure 3** In comparison with baseline, the changes of connectivity strengths between most ROIs had no statistical significance, except increased connectivity strengths in RFC-ROL, RFC-LOL, and RFC-LPL. (**a** and **b**) presented the average connectivity strengths (z-scores) between ROIs at baseline and after moderate sedation, respectively. Yellow color indicated positive connections, and blue color indicated negative connections. The darker color indicated stronger connectivity strength. (**c**) presented the changes of connectivity strengths (t values) between baseline and moderate sedation which was analyzed by paired *t*-test. Yellow color indicated a relative decrease in connectivity strength after moderate sedation, whereas blue color indicated a relative increase in connectivity strengths after moderate sedation. The darker color indicated higher t values. Statistical differences between groups were considered as significance when $|t| \geq -3.25$.
**Abbreviations**: RFC, right frontal lobe; ROL, right occipital lobe; LOL, left occipital lobe; LPL, left parietal lobe; ROIs, region of interests.


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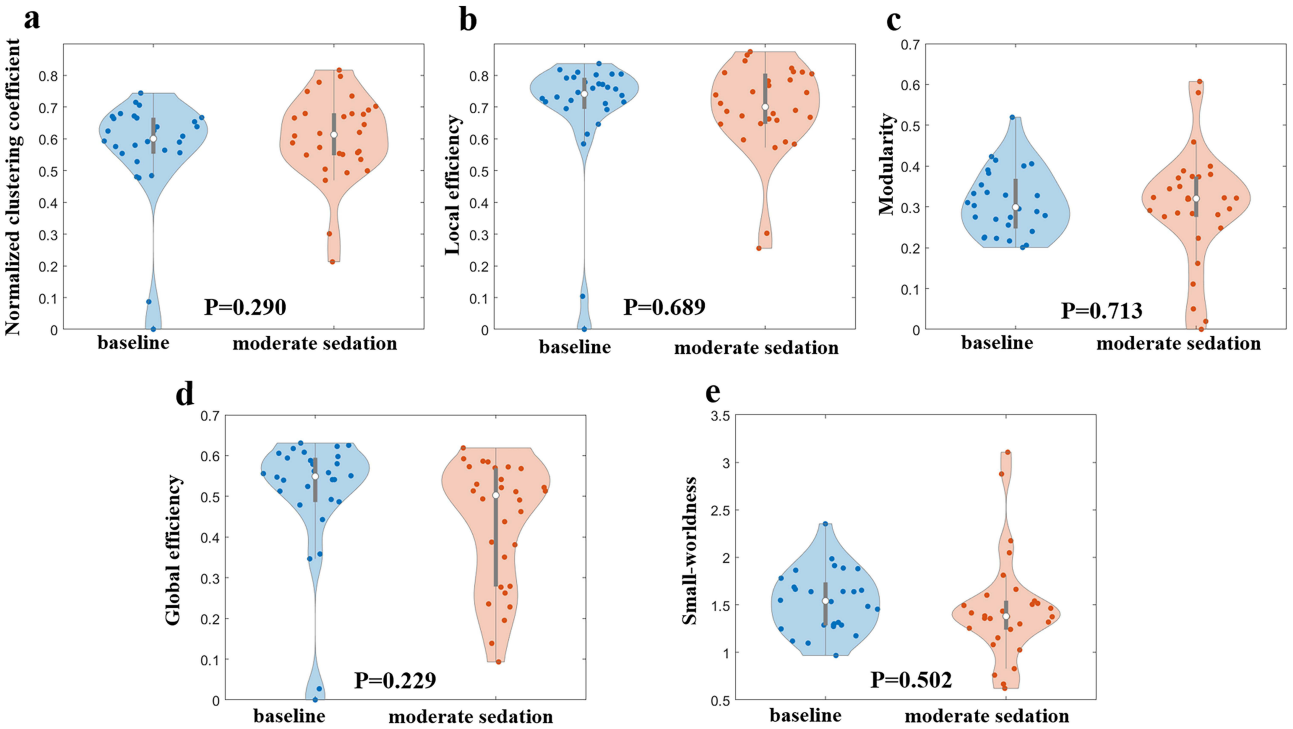


**Figure 4** In comparison with baseline, the normalized clustering coefficient (0.55 ± 0.19 vs.0.60 ± 0.13, P=0.290, (**a**) local efficiency (0.67 ± 0.22 vs.0.69 ± 0.14, P=0.689, (**b**) modularity (0.31 ± 0.08 vs 0.30 ± 0.14, P=0.713, (**c**) global efficiency (0.49 ± 0.18 vs 0.43 ± 0.15, P=0.229, (**d**) and small-worldness (1.53 ± 0.32 vs 1.46 ± 0.56, P=0.502, (**e**) did not show statistical significance after moderate sedation. The white dot represented the median. The upper and lower Poles of the thick line represented the 75% quantile (Q75) and 25% quantile (Q25) respectively. The upper and lower poles of the thin line represented the extreme values. The blue and red graphs represent the kernel density plots at baseline and moderate sedation, respectively.

There are insufficient data to support the dose regimen of remimazolam for moderate sedation in neurosurgical patients. Our study provided supplemental evidence for remimazolam dosage in neurosurgical children. In adult patients undergoing procedural sedation, the ED90 of remimazolam was about 0.19 mg/kg to achieve loss of consciousness which was inversely correlated with age (ie, 0.25mg/kg at 40 years and 0.19mg/kg at 60 years).[7] Our result indicated that children might require a relatively higher dose (about 0.28 mg/kg) for moderate sedation, and this dosage was accompanied by a favorable safety profile in the study. One reason for the higher dose may be attributed to the larger distribution volume of drugs in children.[25] Previous studies on propofol also showed that younger children needed higher dosages for procedural sedation such as 4.8 mg/kg for infants under 1 year and 2.5mg/kg for patients aged 17 years.[26]

In sensitivity analysis, the dosage of remimazolam for moderate sedation had no statistical difference in children of different age groups. Meanwhile, the time to onset of moderate sedation with remimazolam was approximately 10 seconds, indicating that remimazolam was suitable for preanesthetic scenarios and could rapidly alleviate patients' preoperative anxiety.

In this study, a fixed-staircase method (k-in-a-row) derived from the classic up-and-down designs was used for dose finding. Compared with other sequential designs such as the biased-coin method, it presents a unique stationary mode near its target percentile and also displays better operational characteristics.[27]

## The Safety Profile of Remimazolam

The incidence of ED was about 62.2% in this study which seemed to be higher than non-neurosurgical pediatric surgery (ie, 14.9%–38.3%).[28] This might be attributed to the unique characteristics of these children. First, 72.9% of enrolled children were diagnosed as hydrocephalus with nervous system development abnormalities. This increased the risk of ED development.[9] Second, up to 77.4% of children in this study had experienced at least one episode of general anesthesia before. Repeated exposure to anesthesia also increased the risk of ED.[29,30]

In this study, we observed 5 respiratory depression events and all cases were mild, and resolved rapidly with oxygen supplementation. The unique anatomy of children's respiratory system, characterized by low residual lung function and low

cardiopulmonary reserve, makes them less tolerant to hypoxia.[31] Therefore, when administering remimazolam in children, it is crucial to closely monitor respiratory function and provide necessary interventions to avoid hypoxia. One child developed hiccup, but the underlying mechanism of benzodiazepines-associated hiccup was still uncertain.[32] No hypotension, injection pain, and delayed recovery were observed in this study, which was consistent with previous studies.[7]

### Remimazolam-Induced Changes in Brain Network Connectivity

Anesthetics exert significant effects on brain network connectivity which is important for maintaining consciousness and cognition.[33,34] In this study, the changes of connectivity strengths between most ROIs and topological properties of brain network had no statistical significance, except increased connectivity strengths in RFC-ROL, RFC-LOL, and RFC-LPL. There was limited evidence about the effect of remimazolam on brain network connectivity. Previous studies showed that midazolam could lead to a different distribution of cerebral blood flow such as decrement in the right superior and inferior frontal gyrus and increment in the bilateral occipital lobes.[35] This indicated that benzodiazepines might primarily affect the function of the frontal and occipital lobes, which is consistent with the results of this study. In healthy pediatrics, fMRI studies had revealed that mild sedation with midazolam could effectively preserve the lower-order network connectivity including visual, auditory, and sensorimotor functions.[36,37] Our study found that remimazolam sedation enhanced the connectivity strengths between frontal lobe and occipital lobe, as well as parietal lobe. This indicated that remimazolam might have a similar effect on brain network connectivity as midazolam, which mainly compromised the higher-order networks and preserved the lower-order networks located in the occipital and temporal lobes.[38] Children with hydrocephalus may exhibit reduced functional connectivity between the bilateral frontoparietal network and the default mode network, but they may have enhanced connectivity between the right frontoparietal network and the left dorsal attention network across hemispheric regions.[39] The disease-related changes in anatomy and network connectivity might interfere with the interpretation of present result. Further studies are needed to investigate if these changes in brain network connectivity exist in children with normal central nervous system.

## Limitations

This study had some limitations. First, this study found that the ED90 of remimazolam for moderate sedation in neurosurgical children was 0.28mg/kg with wide CI. Although the sample size was estimated based on the Dixon and Massey's formula, the statistical result indicated insufficient sample size. Further studies with large sample size are needed to validate the result. This variability may also be partially influenced by individual developmental differences and the heterogeneity of underlying neurological conditions in neurosurgical pediatrics. Second, this study merely focused on the ED90 of remimazolam for preanesthetic moderate sedation and did not explore its effectiveness and safety in general anesthesia for children. It is notable that the conclusion cannot be directly extrapolated to children undergoing non-neurosurgery. Third, fNIRS indicated that remimazolam might have small effect on brain network function in children undergoing neurosurgery, but further studies are required to generalize this finding to other pediatric groups and to determine if this effect is associated with clinical outcomes (ie, ED).

## Conclusions

This study found that the ED90 of remimazolam for moderate sedation was 0.28 (95% CI 0.24–0.42) mg/kg in children with hydrocephalus or structural brain disease undergoing neurosurgery. These results provide important information for the use of remimazolam in children with neurologic disease, but its application in non-neurosurgical pediatric should be furtherly explored.

## Abbreviations

ED90, 90% effective dose; ED, emergence delirium; fNIRS, functional near-infrared spectroscopy; MOAA/S, modified Observer's Assessment of Alertness/Sedation; CAPD, Cornell assessment of pediatric delirium; m-YPAS, modified Yale preoperative anxiety scale; ROIs, regions of interests; RFC, right frontal lobe; LFC, left frontal lobe; RTL, right temporal lobe; LTL, left temporal lobe; RPL, right parietal lobe; LPL, left parietal lobe; ROL, right occipital lobe; LOL, left occipital lobe; CI, confidence interval; SD, standard deviation; IQR, interquartile; FDR, False discovery rate.

## Data Sharing Statement

All data are publicly available and attached to the paper.

## 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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