Clinical study protocol

To investigate the 90% effective dose (ED90) induced by anesthesia in pediatric painless gastroenteroscopy: an up-and-down sequential test of biased coins

Determination of the ED90 (90% Effective Dose) of Remimazolam Anesthesia Induction in Pediatric Painless Gastrointestinal Endoscopy: A Biased Coin up and Down Sequential Trial

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1. Research background

In recent years, painless digestive endoscopy technology is advancing rapidly in our country.According to a national survey[1]，The volume of digestive endoscopy in our country is increasing year by year, and it is expected that by 2030, the number of digestive endoscopy under sedation will reach 51 million.Pediatric digestive endoscopy tends to have a higher rate of sedation due to low tolerability and adherence in childrenGastroenterologists often choose to use painless gastroenteroscopy to assess gastrointestinal conditions, and its indications include abdominal pain, vomiting, anemia, etc. However, unlike adult painless gastroenteroscopy, children have higher sensitivity to endoscopic stimulation and worse tolerance to hypoxia, which leads to a significant increase in the probability of adverse events in pediatric patients under shallow sedation and deep sedation[2,3]。 So far, propofol is still the preferred procedural sedation drug for clinical application, but its adverse reactions such as hypotension and respiratory depression have made researchers urgently seek better alternatives to meet higher anesthesia requirements[4]。

Remimazolam is a new benzodiazepine drug, which is an ultra-short-acting GABAA(γ-aminobutyric acid subtype A) receptor agonists. It not only retains the characteristics of benzodiazepines, such as water solubility, antagonism, no injection pain, and can be antagonized by flumazenil, but also adds some pharmacological characteristics of remifentanil due to the side chain of methyl propionate in the structure, such as fast onset, short action time, inactivity of metabolites, and not affected by infusion time[5–8]。Studies have shown that,Remimazolam has the clinical advantages of "short", "flat" and "fast", and the patient's recovery time is fast, and the postoperative recovery is faster.The incidence of adverse events such as decreased blood pressure and respiratory depression during gastroenteroscopy is lower and the safety is higher[9]。 The unique pharmacological properties are also suitable for day surgery, precision anesthesia, and accelerated recovery surgery(enhanced recovery after surgery, ERAS)

and other anesthesia concepts, which are suitable for gastroenteroscopy, bronchoscopy and anesthesia induction, and can avoid adverse reactions such as hemodynamic fluctuations, excessive sedation, and injection pain caused by propofol to a greater extent, and the safety is good and better than propofol[10,11]。

Domestic and foreign studies on remimazolam mainly focus on sedation effect and safety, and there are also studies on the appropriate dose of remimazolam induction anesthesia in adults[12,13], but there are fewer studies in pediatric anesthesia. In our previous study, we found that the treatment rate of remimazolam induction anesthesia in pediatric painless gastroenteroscopy was high, and at the same time, the dosage required by children of different ages varied, and infants and young children often required multiple additional medications to cause unconsciousness, reducing the satisfaction of patients and surgeons. shown in a study by George D Politis et al[14]There are indeed differences in the dosage of propofol in induced sedation in children of different ages, and at the same time, it has been shown in related studies of remimazolam[15]In adult patients, the effective sedation dose of remimazolam decreases with age, so it is meaningful and necessary to explore the dosage of sedation drugs in anesthesia induction.

The safety and efficacy of remimazolam in children of different ages have also been confirmed and evaluated by several studies. In preschool children (0-6 years old)Remimazolam has been safe and effective for painless gastroscopy[16], root canal treatment[17], tonsillectomy[18], fiberoptic bronchoscopic lavage[19]and other clinical operations. These results suggest that remimazolam has the advantage of shortening the time to awakening and PACU stay, and reducing the incidence of adverse reactions such as respiratory depression, hypotension, and injection pain, and no serious remimazolam-related adverse reactions were found.In school-age children (7-12 years old)Remimazolam also has a good safety and efficacy[18,20]It can be successfully used for tonsillectomy, supratentorial glioma resection, etc., and the anesthesia process of the child is smooth, which better avoids the occurrence of hypotension and propofol infusion syndrome, reduces the incidence of postoperative agitation, and improves the satisfaction of the child's parents. No other adverse reactions related to remimazolam

were observed.

The latest literature shows[21], it is not recommended to use the traditional Dixon sequential test method to explore the half-effective dose of anesthetic drugs（median effective dose,ED50）Then, statistical principles and formulas were used to calculate the 90% effective dose （the 90% effective dose,ED90）。 In order to avoid computational bias, this study intends to explore remimazolam using the bias coin upper and lower sequential testAnesthesia-induced ED90 and 90 in pediatric gastroenteroscopy at different ages% confidence interval(confidence interval, CI), to provide more clinical reference for the anesthesia induction application of remimazolam.

At the same time, the depth of anesthesia was monitored using the anesthesia depth monitor Narcotrend (NT),NT has the advantages of perfect hierarchy, rapid data processing, unaffected by electromyographic activity, and high reliability[22,23], and its technology for using NT in pediatric procedural sedation is also very mature[24–26]。 Therefore, NT was chosen to monitor the depth of anesthesia to prevent intraoperative inadequacy and to predict and remedy the occurrence of adverse events in time, while providing more credible data for the calculation of ED90 in this study.

2. Research purpose

To explore the ED90 of remimazolam in pediatric gastroenteroscopy in different age groups, and to provide a more scientific clinical dose selection basis for the anesthesia induction application of remimazolam.

3. Research design

This study is a prospective, double-blind, sequential trial.

1. Patient selection

It is planned to observe cases of pediatric painless gastroenteroscopy in Tongji Hospital from March 2024 to December 2024.

2. Sample size calculation

The main observation indicator in this study was the success rate of sedation in

patients. According to the literature, the offset coin method is used（biased-cion design, BCD）Design sequential tests（up-and-down method, UDM）For determination of the ED90 of the drug, the recommended sample size is 50-60 cases[21]。 In this experiment, the patients were divided into three groups according to age[14]：1.Toddler group、2.Preschool group, 3.School-age groupTherefore, this experiment plans to include 165 samples, 55 cases in each group.

3. Inclusion criteria

（1） Age 1-12 years old

（2） ASA Class I-II;

（3） Signed informed consent.

4. Exclusion Criteria

（1） Those with developmental delay, or neuropsychiatric diseases;

（2） Severely malnourished, or severely obese;

（3） Patients with high risk of stomach satiety and reflux aspiration;

（4） Those who are allergic to benzodiazepines and opioids;

（5） Those who have taken sedative, analgesic or antidepressant drugs within 24 hours;

（6） Severe sleep apnea;

（7） Abnormal liver and kidney function;

（8） Recent participation in other clinical studies.

5. Midway exit criteria

（1） Serious adverse events such as major bleeding and intestinal perforation during surgery;

（2） Participant withdraws consent;

（3） Follow-up shedding.

6. Rejection criteria

Enrolled cases that meet any of the following criteria will be excluded and will not be analyzed in the next step.

（1） No use of study drugs;

（2） No research records;

For rejection cases, detailed reasons are recorded and CRFs are kept for reference. The results of these cases are not further analyzed for treatment effects.

4. Research process

1. Preoperative evaluation

Patients will be visited according to clinical routine the day before surgery, enrolled patients will be determined according to the inclusion and exclusion criteria, and the informed consent form will be signed to record the basic information of the patients.

2.Research methodology

The research method of this experiment is biased coin sequential analysis (BCD-UDM).

3. Research process

With the exception of the experimental drug remimazolam, all patients received standardized care and anesthesia management. All children are required to fast for 8 hours, abstain from water for 2 hours, and do not use pre-anesthesia medication before surgery. Grouping: Children are divided into 3 groups according to age, namely 1Toddler group: 0-3 years old (<48 MOS), 2Preschool group: 4-6 years old (≥48 and <84 MOS), 3School-age group: 7-12 years old (≥84 and <156 MOS). （months, MOS）

The experimental drug used in this study was remimazolam benzolate for injection, and the analgesic drug was remifentanil, and the anesthetic drugs were prepared in advance according to the concentration of remimazolam 1mg/ml and remifentanil 1mcg/ml, and ephedrine, atropine and other drugs were routinely extracted for backup.

The child entered the children's digestive endoscopy room after opening the intravenous infusion in the ward, and the mask inhaled oxygen for 3 L/min. Routine monitoring of blood pressure (NIBP), heart rate (HR), blood oxygen saturation (SpO2), electrocardiogram (electrocardiogram (ECG), respiratory rate (RR), and perfusion index (PI). After lateral decubitus, different doses of remimazolam + remifentanil were slowly injected intravenously over 1 minute using a micropump, with a fixed induction

dose of 0.5 mcg/kg of remifentanil. According to the pre-experiment, the initial dose of remimazolam in the toddler group was 0.5 mg/kg, the initial dose was 0.4 mg/kg in the preschool group, and the initial dose was 0.3 in the school-age group mg/kg, and the dose was 0.02 mg/kg at adjacent intervals. According to the BCD-UDM, the dose of remimazolam for the next child is determined based on the response of the previous child, the first patient in each group starts with the initial dose, and after the patient is administered this dose, the loss of consciousness (negative) within 2 minutes is recorded as a failure of sedation, and remimazolam 0.05 mg/kg is added (instruction manual requirements: the maximum additional dose at a time does not exceed 2). .5mg, the maximum number of additions is 5) + remifentanil 0.1 mcg/kg to keep the child quiet and painless. If target sedation is not achieved, 0.5 mg/kg propofol is given as rescue sedation. keep the patient quiet and pain-free, and the next patient will be increased by one dose; In case of loss of consciousness (positive), the next patient's dose of remimazolam remains the same or is reduced by one dose, whether the dose is reduced based on a computer-generated list of partial coin experiments. During the examination, respiratory depression and blood oxygen saturation decreased, and the jaw was supported to assist in respiratory correction; If blood pressure drops significantly and heart rate slows down, ephedrine and atropine are given symptomatic treatment to maintain circulatory stability.

After the examination, the child is transferred to the Post-Anesthesia Care Unit (PACU) to observe the child's respiratory status to confirm that there is no airway obstruction. In the PACU, the child received oxygen via nasal cannula for 2 L/min and was monitored by NIBP, HR, and SpO2. If the Postanesthetic Discharge Scoring system (PADS) score ≥ 9 points after anesthesia, the transfer from the PACU to the ward is confirmed by the attending anesthesiologist.

4.Blinding

In this trial, remimazolam was prepared by an independent anesthesia nurse who was not involved in further clinical management and research, and anesthesiologists, digestive endoscopists and nurses were involved in intraoperative management and postoperative outcome assessment, and neither the patient nor their parents were

informed about the dose of remimazolam.

5. Observe the indicators

1) The main observation indicators were the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) and the Anesthesia Depth Monitoring Index.

2) Secondary observation indicators:

1. Incidence of respiratory depression: respiratory rate < 8 times/min or SpO2 < 90%;
2. Adverse event monitoring: intraoperative blood pressure and heart rate changes: record the patient's intraoperative blood pressure, heart rate, and the use of related vasoactive drugs; Postoperative adverse reactions: such as hypertension, hypotension, tachycardia, gastrointestinal symptoms, postoperative restlessness, etc.
3. anesthesia time, induction time, operation time, recovery time, recovery time;
4. the total amount of sedative and analgesic drugs used;
5. Postoperative pain (FLACC Pain Assessment Scale, FLACC pain score): The FLACC score was assessed at different time points in the PACU (0 minutes after awakening, 10 minutes after awakening) and within 24 hours after surgery.
6. Postoperative nausea and vomiting (PONV) (BARF score: Buster retching facial scale score): PONV was assessed until discharge.
7. 24 hours postoperative follow-up: The children and their parents were asked to score their sleep quality, daily activities, and parental satisfaction after surgery.

5. Statistical Analysis Plan

Probit regression analysis was used to calculate the probabilistic regression equation of remimazolam in pediatric painless gastroscopy anesthesia induction, and the fit test was carried out, and finally the ED90 and 90% CI of remimazolam in pediatric painless gastroscopy were calculated according to the equation. SPSS 25.0 statistical software was used for data analysis, and the mean ± standard deviation of the continuous data was used, and the analysis of variance or paired t-test was used. Count data are

expressed as percentages and the χ^2 test is used. *$P<0.05$ was a statistically significant difference.*

Six. schedule

1. Improved MOAA/S scoring scale

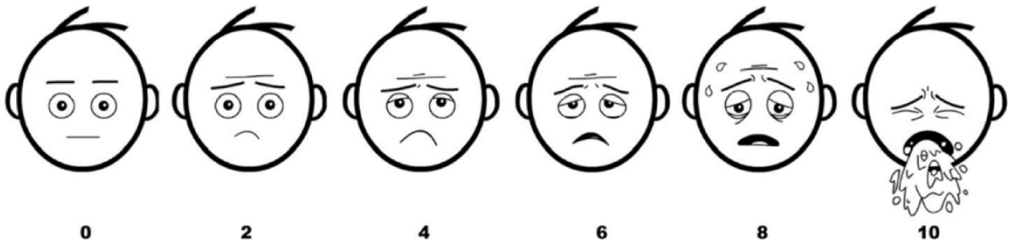
fraction	Reaction description
5	Respond quickly to names spoken in a normal tone
4	Exhibit a drowsiness response to names spoken in a normal tone
3	React only after calling the name aloud and/or repeatedly
2	React to slight irritation or shaking
1	Responds only after a painful trapezius muscle squeeze
0	The trapezius muscle does not respond after squeezing

2. FLACC behavioral rating scale

content		Score
facial expression	No specific expression or smile	0
	Occasional facial distortion or frowning	1
	Constant trembling of the chin, constriction of the jaw, frowning	2
Leg activity	Normal position or relaxed state	0
	Discomfort, inability to rest, muscle or nerve tension, intermittent flexion/stretching of the muscle	1
	Kicking or straightening the waist, high tension, expanding the flexion/extension of the body, shaking	2
Position	Lie quietly and in a normal position, and can move smoothly	0
	Hurried and restless, moving back and forth, nervous, hesitant to move	1
	Curling or spasms, swinging back and forth, shaking the	2

	head from side to side, rubbing a part of the body	
Crying	Don't cry or make trouble	0
	Moaning or sobbing, occasionally crying, sighing	1
	Constantly crying, screaming or sobbing, moaning	2
comfortable	Calm, content, relaxed, not demanding comfort	0
	Occasional physical contact can dispel doubts and distract attention	1
	Comfort is difficult	2
Score		divide

3. BARF Scoring Table:



fraction	Reaction description
10	Vomiting POV
6-8	Severe PON
2-4	Mild PON
0	not

4. Postoperative sleep quality score table:

fraction	Reaction description
0	Sleep well
1	Waking up at night crying
2	Intermittent sleep

5. Daily activity scoring table:

fraction	Reaction description
0	Normal quality
1	Depressed but performing normal daily activities
2	Irritability and inability to perform normal activities

6. Parental Satisfaction Score: The score ranges from 0-10, with 10 indicating the highest level of satisfaction.

7. PADS scoring table:

standard	fraction
Vital signs	
Fluctuations were within 20% of the preoperative measurement for both blood pressure and pulse	2
Fluctuations in blood pressure and pulse are within 20-40% of the preoperative measurement	1
Fluctuations occurred when both blood pressure and pulse were outside 40% of preoperative measurements	0
activity	
Steady bearing and gait determination, or return to preoperative baseline levels	2
Able to determine orientation or steady gait	1
Cannot meet any of the first two	0
Nausea and vomiting	
Very few	2
Moderate	1
Severe	0
pain	
Very few	2

Moderate	1
Severe	0
Surgical bleeding	
Very few	2
Moderate	1
Severe	0

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