Subject number

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

Principal investigator: Xu Aijun, associate professor, chief physician

Research subjects: Cases of pediatric painless gastroenteroscopy planned to be performed in Tongji Hospital in an elective period

This informed consent form contains two parts:

• Informed part (informing relevant information related to this study).

Please read this form carefully. It contains important information related to this project. One of the members of our project team will tell you more about the study. Participants who agree to participate in this study are referred to as "subjects". The title "subject" has been used throughout the informed consent form.

• Signed consent (if agreed to participate in this study).

If you have any questions about this study, please consult us. It is entirely your decision to participate in this study. If you decide to participate in this study, please sign this informed consent form.

Part 1: Knowing

objective

In recent years, painless digestive endoscopy technology has been advancing rapidly our country, according to a national survey, the number of our country digestive endoscopy is increasing year by year, and it is expected that by 2030, the number of digestive endoscopy under sedation will reach 51 million. Due to low tolerance and compliance in children, the sedation rate of pediatric digestive endoscopy is often high, and gastroenterologists often choose to evaluate gastrointestinal conditions with painless gastroenteroscopy, 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 too deep sedation. 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.

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.Studies have shown that,Remimazolam has a "short",The clinical advantages of "flat" and "fast",The patient has a quick recovery time and faster recovery after surgery;The incidence of adverse events such as decreased blood pressure and respiratory depression during gastroenteroscopy is lower and the safety is higher. 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。

Domestic and foreign studies on remimazolam mainly focus on sedation and safety, and there are also appropriate dosage studies on the use of remimazolam to induce anesthesia in adults, but there are few 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. The study of George D Politis et al. showed that there is indeed a difference in the dosage of propofol in induction of sedation in children of different ages, and at the same time, the relevant study of remimazolam showed that in adult patients, the effective sedation dose of remimazolam decreases with age, so it is meaningful and necessary to explore the dosage of sedation 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, root canal treatment, tonsillectomy, fiber bronchoscopic lavage 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 good safety and efficacy, and can be successfully used for tonsillectomy, supratentorial glioma resection, etc., the anesthesia process of the child is stable, the occurrence of hypotension and propofol infusion

syndrome is better avoided, the incidence of postoperative agitation is reduced, and the satisfaction of the child's parents is improved. No other adverse reactions related to remimazolam were observed.

The latest literature suggests that it is not recommended to use the traditional Dixon sequential test method to explore the median effective dose (ED50) of anesthetic drugs, and then use statistical principles and formulas to calculate the 90% effective dose (ED90). In order to avoid computational bias, this study intends to explore the ED90 and 90% confidence interval (CI) of remimazolam in pediatric gastroenteroscopy at different ages using the biased coin upper and lower sequential test method, so as to provide more clinical reference for the anesthesia induction application of remimazolam.

At the same time, the depth of anesthesia monitor Narcotrend (NT) was used to monitor the depth of anesthesia, and NT has the advantages of perfect hierarchy, rapid data processing, not affected by electromyographic activity, and high reliability, and its technology for using NT in pediatric procedural sedation is also very mature. 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.

The purpose of this study is 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.

Subject selection

We invited all children who planned to undergo elective painless gastroenteroscopy in Tongji Hospital to participate in the trial.

Inclusion Criteria

（1） Age 1-12 years old

（2） ASA Class I-II;

（3） Signed informed consent.

Exclusion Criteria

(1) Those with developmental delay or neuropsychiatric diseases;

(2) Those who are 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;

Subject number

(8) Recent participation in other clinical studies.

Volunteer to join:

Participation in this study is completely voluntary. It's up to you to participate or not. Whether you end up enrolling your child in this trial or not, there will be no difference in the care your child receives while in the hospital. If you decide to join this study, you can change your mind and give up participating at any time during the study process afterwards.

Information about remimazolam

Remimazolam is a novel benzodiazepine drug that is an ultra-short-acting GABAA receptor agonist. It not only retains the characteristics of benzodiazepines, such as water solubility, antagonistic resistance, no injection pain, etc., 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. Remimazolam has a fast onset of action, high safety, does not rely on specific organ metabolism, and can be quickly cleared even after prolonged infusion. Renal insufficiency does not affect the pharmacokinetics of remimazolam. Based on these unique pharmacological effects, we hypothesize that remimazolam should be a reasonable choice for painless gastroenteroscopy in children.

Study protocol:

All children received standardized care and anesthesia management, except for the experimental drug remimazolam. All children are required to eat liquids as much as possible the day before, fast for 6-8 hours before the examination, and abstain from water for 2 hours. No pre-anesthetic medication. Grouping: Children are divided into 3 groups according to age, namely 1Toddler group: 1-3 years old (≥12 and <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 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), pulse oxygen saturation (SpO2), and electrocardiogram(electrocardiogram, ECG), respiratory rate (RR), and perfusion index (PI). After lateral decubitus, different doses of remimazolam + remifentanil were injected intravenously by a micropump within 1 minute, and the fixed induction dose of remifentanil was 0.5 mcg/kg. 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 in the second child is determined based on the response of the previous child, the first patient in each group starts from the initial concentration, and after the completion of this dose, the patient loses consciousness within 2 minutes (negative) is recorded as a sedation failure, and remimazolam 0.05 mg/kg is added (instructions require that 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 through a 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 attending anesthesiologist confirms the transfer from the PACU to the ward.

Our researchers will closely care and care for your child throughout the trial. If you have any concerns or concerns during this process, you can communicate with our researchers.

Protocol: Depending on your child's condition, we will treat him according to clinical medical practice guidelines, which means that regardless of whether your child ends up participating in this study or not, he will receive the exact same medical care, and once your child is accepted into our study, the relevant

The day before surgery (screening): This visit will take approximately 1 hour, we will test your child according to the protocol requirements to determine if we meet our inclusion criteria, we will:

- Ask about your child's medical history
- Have your child examined
- Check and record your child's vital signs
- Extract information from your child's case profile
- Assess your child's risk of surgery

Before and during surgery:

- Relevant case data were recorded before and during surgery

Postoperative observation:

- Analgesic scores, nausea and vomiting and complications were collected at 0 min and 10 min after awakening

Follow-up:

At 24 h after the end of the operation, we collected the following information by going to the ward for follow-up:

- Postoperative complications
- Pain scores, nausea and vomiting
- Daily activity scoring
- Sleep score
- Parent satisfaction score

Research period

The entire study cycle lasts for 24 hours, during which you need to be followed up once, and the follow-up time is about 3-5 minutes.

Adverse reactions and risks

Throughout the trial, your child will receive standardized treatment according to guidelines. If your child is enrolled in this study, the risks and adverse effects are only related to the use of the trial drug.

Remimazolam is a novel benzodiazepine drug that is an ultra-short-acting GABAA receptor agonist. Remimazolam has a fast onset of action, high safety, does not rely on specific organ metabolism, and can be quickly cleared even after prolonged infusion. However, there are cases of

hypotension, dizziness, vomiting reactions, usually this reaction does not have a serious impact on the child, at the same time, studies have shown that remimazolam has a lower incidence of adverse reactions (such as hypotension, injection pain, etc.) compared with painless gastroenteroscopy commonly used sedative drugs, therefore, We reasonably hypothesize that remimazolam is a more suitable anesthetic sedative for painless gastroenteroscopy in children. The entire study process is closely monitored, and if we suspect serious adverse reactions related to remimazolam during the course of the trial, the researchers will also interrupt the use of your child's medication without your consent, including:

- Severe hypotension
- dizzy
- Nausea and vomiting

Benefit

If you accept this study, your child may get a smoother anesthesia, fewer adverse anesthesia reactions, faster anesthesia recovery time, help the endoscopist complete the operation faster and better, and at the same time, your participation will greatly help us answer medical questions and benefit later patients.

confidentiality

If you participate in this study, your child's medical information may be known to others, but the identity of the subject will be kept confidential. The case data we collect during the trial will be completely confidential, we will name your child's profile numerically, and your and your child's name information will not appear in the profile file. Your and your child's information will be kept in a safe and in a database that requires authentication. Only the researcher, your child's doctor, our partners and data checkers have access to your information.

Refusal and exit midway

If you refuse to participate in this study, it will not affect your child's other rights and benefits enjoyed by our treatment. You can also withdraw from this study at any stage of the study without reason, and your child's treatment will not be affected in any way. Your choices and rights will always be respected.

Study the cost description

The normal fee for the use of drugs in this study is not added, and no additional examination and transportation costs are added.

Research related injury treatment and compensation/compensation

(1) Prevention and treatment measures: After the child enters the operating room, the vein is routinely opened, 250 ml of 5% glucose solution is infused, vital signs are closely monitored during the operation, and if hypotension occurs (mean arterial pressure drop>s to 20% at baseline and lasts > 10 minutes), an appropriate amount of crystalloid fluid supplementation and/or ephedrine intravenous push is given. Use other vasoactive drugs and benzodiazepine antagonist flumazenil as needed, and record the medication in detail. Previous studies have found that remimazolam and remifentanil are administered in combination, and patients hardly experience nausea and vomiting in the perioperative period. If respiratory depression occurs during surgery and blood oxygen saturation decreases, the lower jaw should be supported to assist breathing for correction. Endotracheal intubation controlled ventilation if necessary.

(2) Compensation/compensation: The relevant treatment drugs used (such as benzodiazepine antagonist flumazenil and other rescue drugs, etc.) are free of charge, and the increased hospitalization costs due to anesthesia-related complications will be compensated accordingly. The liability for compensation shall be borne by the project team undertaking the study.

Contact information

At any stage, if you have any questions, you can ask our researchers, here are the relevant contact details:

Xu Aijun Associate Professor, Chief Physician, Phone:15927049734 , Mailbox:ajxu@tjh.tjmu.edu.cn

Part 2: Agree

My child and I were invited to participate in a study investigating the 90% effective dose (ED90) of remimazolam induced by anesthesia in pediatric painless gastroenteroscopy: a biased coin up and down sequential trial. I was told that my child would be sedated with remimazolam and 1 follow-up, and I was told that the risk of using remimazolam was low. At the same time, I know that we cannot gain anything else for me and my children. At the same time, I already know the contact information of the researcher, and I can communicate with him at any time if I have any questions.

I have read/been informed of the following information and I have had the opportunity to consult questions about this study and my questions have been answered satisfactorily. I am now volunteering for this study and am aware that I have the right to withdraw at any stage of

Subject number

the study, affecting my other rights and interests.

Subject's name _____ and hospitalization number _____

Signed by the legal guardian _____

Date (year/month/day) _____

If the subject's guardian is illiterate, the fingerprint is pressed to indicate consent.

Fingerprint of the legal guardian: _____ (such as the index finger of the right hand.)

Date (year/month/day) _____

I have read or witnessed that the informed consent form has been read to the potential subject accurately, the subject has asked relevant questions, and I certify that the subject's participation in this study is completely voluntary.

Researcher's name _____

Signed by the investigator_____

Date (year/month/day) _____