Project summary

Preoperative fear and anxiety are prevalent in children undergoing surgery. Midazolam has been generally used as a premedication, and compellent data regarding effective dose to mitigate anxiety is lacking. The current trial addressed the comparable efficacy of intravenous midazolam with different doses regarding the anxiety state, ease of child-parental separation, and mask compliance as premedication in pediatric patients undergoing tonsillectomy. The enrolled pediatric patients are randomly assigned to one of the three groups: receive intravenous 0.03 mg/kg midazolam (group A), 0.05 mg/kg midazolam (group B), or saline control (group C), 40 minutes before surgery. The primary outcome is the level of sedation following the intervention until 40 minutes after premedication, as measured by the modified Yale preoperative anxiety scale (mYPAS) and sedation scale (SS). Secondary outcomes include onset time of sedation, the successful rate of peripheral intravenous cannulation, parental separation anxiety (PSAS), compliance of mask induction (MAS), wake-up time, and duration of stay in the post-anesthesia care unit (PACU), and premedication-related adverse effects. We expect that intravenous administration of a single dose of midazolam 0.05 and 0.03 mg/kg produces similar effects on sedation status, parental separation, and mask induction acceptance, except for rapid-onset and long sedation duration in pediatric patients premedicated with 0.05 mg/kg midazolam.

General information

Title: Premedication with Intravenous Midazolam: Efficacy on Preoperative Anxiety and Mask Compliance in Pediatric Patients

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Rationale & background information

Pediatric surgery patients frequently experience preoperative anxiety, which is associated with adverse outcomes as it raises stress indicators, promotes hemodynamic oscillations, and has deleterious effects on postoperative recovery. Premedication is used to help children and their parents cope with the stress of surgery while also making separation easier. Pediatric premedication has been reported to involve various procedures and medicines, with intravenous midazolam being one of the more commonly investigated approaches.

Midazolam, a lipophilic imidazobenzodiazepine, acts as a sedative that also has an anterograde amnestic effect. Rapid onset, especially via the intravenous route (2-3 minutes), limited duration of action (45-60 minutes), and lack of major adverse effects make midazolam a preferred choice for premedication by pediatric anesthesiologists. However, few clinical studies have assessed the efficacy of intravenous midazolam

for sedation in pediatric individuals undergoing elective surgery at various dosages.

Study goals and objectives

This clinical trial aims to evaluate the effects of different intravenous midazolam doses (0.03 or 0.05 mg/kg) on sedation status, parental separation satisfaction, and mask acceptability in adolescents under general anesthesia.

The primary outcome is the level of sedation following the intervention until 40 minutes after premedication, as measured by the modified Yale preoperative anxiety scale (mYPAS) and sedation scale (SS). Secondary outcomes include onset time of sedation, the successful rate of peripheral intravenous cannulation, parental separation anxiety (PSAS), compliance of mask induction (MAS), wake-up time, and duration of stay in the post-anesthesia care unit (PACU), and premedication-related adverse effects.

Study design

This study is a randomized controlled interventional trial.

Children aged 2–8 years, with ASA physical status I-II, will be scheduled for elective tonsillectomy under general anesthesia. Exclusion factors included parents' refusal to participate in the trial, non-elective surgery, congenital abnormalities, allergy to benzodiazepines, and psychological or respiratory issues.

Methodology

Consecutive patients will be randomly assigned to the following three groups: intravenous midazolam 0.03 mg/kg, 0.05 mg/kg, and saline control. A computer-generated randomization table is used to randomize in a 1:1 ratio. An independent nurse staff team not involved in the trial will recruit, screen, and perform the randomization and drug preparation in identical syringes. By sealing the group assignments in opaque envelopes that are sequentially numbered, the parents or legal guardians, the involved anesthesiologist and surgeons, and the data collection technicians will be all blinded.

General anesthesia will be initiated with 3 mg/kg propofol, 3 μg/kg fentanyl, 0.6 mg/kg rocuronium, and then intubated for airway control during surgery. Anesthesia maintenance was achieved by inhaling 50% oxygen and 3% sevoflurane with 2 L/min fresh gas and 0.2 μg/kg/hour remifentanil infusion. Standard monitoring included mean blood pressure (MBP), electrocardiogram (ECG), SpO_2, HR, temperature, and end-tidal anesthetic gas measurements. Ventilation frequency and tidal volume were set to control the pressure of end-tidal carbon dioxide ($PetCO_2$) within the range of 35±5 mmHg. HR and MBP during surgery were titrated within a 30% fluctuation around baseline with vasoactive medications. Immediately after the procedure, the intubated children were transferred to the postanesthesia care unit (PACU), where they were monitored and provided individualized medical care by an independent attending anesthetist. The children were discharged to the ward when complete recovery was achieved as Aldrete’s score reached 10 based on consciousness, mobility, breathing, blood pressure, and SpO_2.

The primary outcome is the level of sedation after receiving the research medication. The modified Yale Preoperative Anxiety Scale (mYPAS) and the sedation scale (SS) were used to assess the level of sedation at 10, 20, 30, and 40 minutes following intranasal premedication. The mYPAS consists of five items: activity, emotional expressivity, level of arousal, vocalization, and parental use. Each item includes four categories except for vocalization, which has six categories. The sum of each category's partial scores is divided by the total number of categories in that item. The summarized scores of five items are then multiplied by 20. No or mild anxiety is indicated by a score of 23.5–30, while severe anxiety is indicated by >30.

Secondary outcomes include sedation onset, emotional state during venous cannulation, parental separation anxiety, mask induction acceptance, wake-up time, duration of stay in the PACU, and premedication-related adverse effects. Sedation onset time is determined as the duration from premedication administration until the time the child complained of dizziness or drowsy, or the SS score reached 3 points. A trained nurse anesthetist, masked to the group assignment, will perform venous cannulation with at least three years of clinical experience. Regardless of whether the vein will be cannulated on the first attempt or not, successful venous cannulation is defined as an emotional state score (ESS) of no more than 2 points at the attempted cannulation. Parental separation anxiety will be assessed using the parental separation anxiety scale (PSAS) during the transfer from the premedication center to OR according to four levels. A satisfactory sedative effect at separation will be considered as PSAS no more than 2 points. The mask compliance is graded on a four-point scale according to the mask acceptance scale (MAS). The percentage of children with "satisfactory" scores of parental separation anxiety is recorded separately in each group. The heart rate (HR), mean blood pressure, sedation level, and medication-related adverse effects will be observed and recorded every 5 minutes. An anesthesia nurse who is unaware of the administered drug and not involved directly in the patients' care will rate and record study data.

The modified Yale Preoperative Anxiety Scale (mYPAS):

A. Activity

1 = Looking around, curious, playing with toys, reading (or other age-appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment.

2 = Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality.

3 = Moving from toy to parent in unfocused manner, nonactivity-derived movements; frenetic/frenzied movement or play; squirming, moving on table, may push mask away, or clinging to parent.

4 = Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent, desperate clinging.

B. Vocalizations

1 = Reading (nonvocalizing appropriate to activity), asking questions, making comments,

babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond.
2 = Responding to adults but whispers, “baby talk,” only head nodding.
3 = Quiet, no sounds or responses to adults.
4 = Whimpering, moaning, groaning, silently crying.
5 = Crying or may be screaming “no.”
6 = Crying, screaming loudly, sustained (audible through mask).
C. Emotional expressivity
1 = Manifestly happy, smiling, or concentrating on play.
2 = Neutral, no visible expression on face.
3 = Worried (sad) to frightened, sad, worried, or tearful eyes.
4 = Distressed, crying, extremely upset, may have wide eyes.
D. State of apparent arousal
1 = Alert, looks around occasionally, notices or watches what anesthesiologist does with him/her (could be relaxed).
2 = Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult.
3 = Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tensed.
4 = Panicked whimpering, may be crying or pushing others away, turns away.
E. Use of parents
1 = Busy playing, sitting idle, or engaged in age-appropriate behavior and does not need parent; may interact with parent if parent initiates the interaction.
2 = Reaches out to parent (approaches parent and speaks to otherwise silent parent), seeks and accepts comfort, may lean against parent.
3 = Looks to parents quietly, apparently watches actions, does not seek contact or comfort, accepts it if offered or clings to parent.
4 = Keeps parent at distance or may actively withdraw from parent, may push parent away or desperately clinging to parent and will not let parent go.

Safety considerations

Before premedication, continuous monitoring with non-invasive blood pressure, electrocardiograph, and pulse oximetry will be conducted. All patients will be observed for 40 minutes after receiving intranasal premedication before being transferred into the OR on a transferring bed. The heart rate (HR), mean blood pressure, sedation level, and medication-related adverse effects will be observed and recorded every 5 minutes.

Follow-up

An anesthesia nurse who is unaware of the administered drug and not involved directly in the patients’ care will rate and record study data. The patients will be monitored for 40 minutes after intervention. On the next day of surgery, an anesthesia nurse will visit the parents and inquire about the surgical experience.

Data management and statistical analysis

The data are displayed as the mean with standard deviation (SD), numbers with percentage, or median with interquartile range (IQR) according to the data distribution. Analysis of variance (ANOVA) will be used to compare three groups regarding demographic characteristics and hemodynamic parameters at different times following the operation. The Kruskal-Wallis test will be performed to compare three groups based on sedation status, mask acceptability, and ease of separation. Furthermore, ANOVA for repeated measurements will be utilized to assess the fluctuation of hemodynamic variables at various time points. The summarized results will be illustrated in tables or figures. All data analysis will be processed with SPSS 25.0 software package (IBM SPSS Inc., Armonk, USA), and all test of statistical significance will be inferred at two-tailed $P < 0.05$.

Quality assurance

WX. Li and JE. Jia will oversight the investigation process with quality assurance system according to GCP regulation.

Expected outcomes of the study

The results of the study can guide clinicians in the use of preoperative medications, dosing, and alerting physicians to possible adverse effects.

Ethics

The study was conducted with the approval of the institutional review board of the Eye, Ear, Nose and Throat hospital affiliated with Fudan University in Shanghai, in accordance with declaration of Helsinki. The experiment was registered at http://ClinicalTrials.gov (NCT04266340).

Informed consent forms

After being informed about the study's aim and protocol, each participant's parents or legal guardians will provid written informed consent for participation.

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