Original Article

Efficacy of premedication with intravenous midazolam on preoperative anxiety and mask compliance in pediatric patients: a randomized controlled trial

Hui Qiao[#], Jing Chen[#], Peipei Lv, Zhou Ye, Yu Lu, Wenxian Li, Jie Jia

Department of Anesthesiology, Eye & ENT Hospital, Fudan University, Shanghai, China

Contributions: (I) Conception and design: J Jia; (II) Administrative support: W Li; (III) Provision of study materials or patients: Y Lu; (IV) Collection and assembly of data: J Chen, P Lv, Z Ye; (V) Data analysis and interpretation: H Qiao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wenxian Li; Jie Jia. Department of Anesthesiology, Eye & ENT Hospital, 83 Fenyang Rd., Shanghai 200031, China. Email: liwenxian@eentanesthesia.com; jiajie@eentanesthesia.com.

Background: To alleviate anxiety before surgery is a significant concern for the pediatric anesthesiologist. Midazolam has been generally used as a premedication, and compelling 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.

Methods: Three hundred and twelve children aged 2–8 years were randomly assigned, 104 per group, to 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. We assessed the anxiety state every 10 min after premedication with modified Yale preoperative anxiety scale (mYPAS), evaluated the emotional state during separation with parental separation anxiety scale (PSAS), and compared their compliance to mask oxygen supply with mask acceptance score (MAS).

Results: Children premedicated with 0.05 mg/kg midazolam achieved a sedated state more rapidly than those who received 0.03 mg/kg midazolam (5.9±2.3 *vs.* 7.0±3.9, P=0.02). The proportion of satisfactory parental separation and compliance to mask ventilation was not different between midazolam groups, which was superior to saline control. The children receiving 0.05 mg/kg midazolam stayed longer in postoperative care unit than those receiving 0.03 mg/kg midazolam and saline. The incidence of postoperative adverse events was rare and comparable among groups.

Conclusions: 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.

Trial Registration: ClinicalTrials.gov NCT04266340.

Keywords: Anxiety; pediatrics; premedication; midazolam; sedation

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Introduction

Pediatric surgery patients typically exhibit anxiety, uncooperativeness, and fear when separated from their parents or presented with a breathing mask, which is associated with psychological disturbance, poor compliance or surgery cancelation, detrimental influence on postoperative recovery, or other potential long-term

psychological implications (1,2). Sedation with various medicines, preoperative parent-child psychological preparation, enriched environment with toys in the preparation room, and group training to build positive interaction between children and medical professionals are proposed to be feasible and effective strategies for reducing children's anxiety (3,4). The administration of sedatives prior to entering the operation room is the most common approach to alleviate the child's distress and allow for smooth anesthesia induction. Researchers have been consistently exploring the proper drugs and the suitable dose of minimal premedication to ensure a calm child for a scheduled procedure.

Midazolam, a lipophilic imidazobenzodiazepine, acts as a sedative that also has an anterograde amnestic effect. Rapid onset, especially via the intravenous route (2–3 min) (5), limited duration of action (45–60 min), 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. Administered intravenous doses may vary from 0.03–0.08 mg/kg (6-9), with 0.05 mg/kg being the most commonly administered dose in daily practice (10). This clinical trial aims to evaluate the following effects of two intravenous midazolam premedication (0.03 or 0.05 mg/kg) in pediatric patients under general anesthesia: (I) anxiety status as primary outcome assessed with the modified Yale Preoperative Anxiety Scale; (II) sedation onset time determinated by the sedation score; (III) parental separation satisfaction according to the parental separation anxiety scale; (IV) mask acceptability evaluated using the mask acceptance scale. We hypothesized that large dose of midazolam results in faster onset time and longer sedation duration. We present the following article in accordance with the CONSORT reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-161/rc).

Methods

Enrollment and eligibility

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This double-blind parallel-group clinical trial was conducted at the Eye and ENT Hospital of Fudan University with the approval of institutional ethics committee (No. 20180341) and was registered at ClinicalTrials.gov (NCT04266340). After obtaining the parent's or legal guardian's approval, informed consent was signed after providing all pertinent details. The study's inclusion criteria were children aged between 2 and 8 years old, American Society of Anesthesiologists (ASA) grade I, scheduled for elective tonsillectomy under general anesthesia. Exclusion factors included parents' refusal to participate in the trial, non-elective surgery, congenital abnormalities, respiratory issues, allergy to benzodiazepines, and psychological disorders (including behavior disorders, mood disorders, hyperactivity syndrome, autism, and developmental delays).

Randomization and masking

A computer-generated random array sealed, and envelope method was employed to divide enrolled pediatric patients into three groups by simple randomization (1:1:1 ratio allocation). Three pediatric surgeons were included in the surgical team that performed the procedures. The experimental medications were prepared and provided by research staff who were not directly involved in patient care, while involved surgeons, responsible anesthesiologists, and participating families were blind to the medication distribution and group allocation. While completing scoring sheets of mask acceptance based on the numbers assigned in the operation theatre, one of the research staff responsible for recording sedations and separation status scores was unaware of the group assignment.

Premedication and administration of anesthesia

The children were required to fast for eight hours. One of the parents escorted the children to a preanesthesia preparation room about 1 h before the procedure. Oxygen saturation (SpO_2) and heart rate (HR) were monitored continuously before receiving premedication.

Patients received intravenous midazolam 0.03 mg/kg, 0.05 mg/kg, and saline control in Group A, B, and C, respectively. Above mentioned vital parameters were collected every 5 min until anesthesia induction. Then the pediatric patients were transferred on the gurney to the operating room, where they were anesthetized 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/h 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.

Outcomes assessment

Preoperative anxiety status, the primary outcome of this study, were evaluated immediately before and at 10, 20, 30, and 40 min after premedication according to the modified Yale Preoperative Anxiety Scale (mYPAS). The mYPAS is validated as an observational tool for assessing children's anxiety between 2–12 years of age, including 24 items, categorized into five domains: activities, emotional expressivity, state of awareness, vocalization, and interaction with parents. Scores greater than or equal to 30 indicate the presence of anxiety (11). To ensure inter-rater reliability, all members of the research panel were instructed to acquire and score the tools. After medication administration, a trained staff member, blind to group allocation, evaluated anxiety status every 10 min until 40 min after premedication.

The time of sedation onset was also recorded, which was defined as the time between when the drug was administered and when the sedation score (SS) reached three points, which were labeled as calm, drowsy, or asleep. When the children had to be separated from their companying parents, anxiety scores were determined in four levels according to the parental separation anxiety scale (PSAS). PSAS no more than two points was labeled as satisfactory separation, when the patients were cooperative, unafraid, or slight fear but easy to ease. The behavioral reaction of the children presented with a breathing mask was scored on a four-point mask acceptance scale (MAS): 1, easy to accept the mask; 2, slight fear of mask, easy to comfort; 3, moderate fear of mask, difficult to calm through comfort; 4, terrified, crying or struggling (12). A trained nurse anesthetist, blind to the group assignment, rated PSAS and MAS score. Other patient data were also recorded and compared, including demographic information, the hemodynamic state, and then every 10 min until anesthetic induction. Discharge time was recorded as when the PACU anesthetist assessed the Aldrete recovery score of 10.

Sample size and statistical analysis

The sample size for each 100-child group was calculated prior to the investigation using a statistical procedure based on 80% power, type one error of 5%, and the data of a previous study (13).

The demographic data, sedation onset time, satisfactory separation, extubation time, PACU time, and PACU adverse events are expressed as the mean ± standard deviation (SD), numbers, or percentages. PSAS and MAS are presented as median with interquartile range (IQR). The results of mYPAS were illustrated in the figure and expressed as box and whiskers plots. Comparisons among three experimental groups were conducted using one-way ANOVA for data with normal distribution or Kruskal-Wallis test for non-normal distributed data. Furthermore, ANOVA for repeated data was performed to analyze the trend of hemodynamic parameters following premedication at different times. All statistical analyses and graphic design were performed with SPSS 25.0 (IBM, SPSS) and GraphPad Prism version 9.0 (GraphPad Software), and a two-sided P values <0.05 were considered statistically significant.

Results

Participants characteristics

A total of 320 children (aged 2–8 years; 182 boys, 138 girls) considering the inclusion were candidates for elective surgery from December 2020 to November 2021. Three children were excluded from the study due to decline to participate in 1 patient and upper airway infection on the day of surgery in 2 patients. As illustrated in the *Figure 1*, however, 2 and 3 patients in the midazolam 0.05 mg/kg and placebo group were ruled out due to the cancellation of the procedures, respectively. As a result, 312 patients were divided into three 104-individual groups at random. *Table 1* displays the demographic data and perioperative parameters, and statistical tests revealed that there were no statistically significant differences in age (P=0.118), weight (P=0.148), or gender (P=0.528) among the three groups.

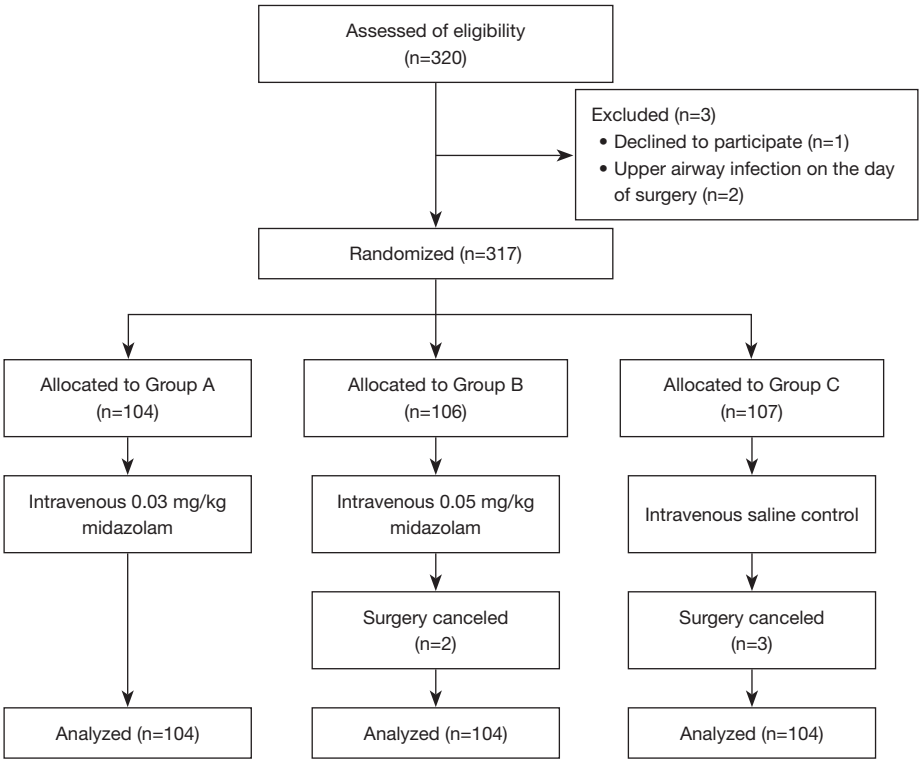

Figure 1 Consort flow diagram.

Table 1 Demographic characteristics

Characteristics	Group A (n=104)	Group B (n=104)	Group C (n=104)	P value
Sex (male/female)	55/49	58/46	63/41	0.528
Age (years)	5.2±1.8	5.1±1.5	5.6±1.7	0.118
Weight (kg)	19.0±4.5	20.1±6.0	20.3±5.0	0.148
Height (cm)	1.1±0.1	1.1±0.1	1.1±0.1	0.155
Body mass index (kg/m^2)	15.7±2.2	15.4±1.9	15.7±2.1	0.658
ASA physical status (I/II)	99/5	96/8	94/10	0.409
Operation duration (min)	42.9±18.7	43.9±17.4	44.1±17.0	0.866
Operator (1/2/3)	55/39/10	63/33/8	47/50/9	0.188

The values are presented as the mean ± standard deviation, or the number of patients. Group A, 0.03 mg/kg midazolam; Group B, 0.05 mg/kg midazolam; Group C, saline control. ASA, American Society of Anesthesiologists.

Sedation status

Before medication, mYPAS among the three groups presented no statistically significant difference with median (IQR) of 45.0 (41.7–58.3), 46.7 (37.9–58.3) and 45.0 (41.7–58.3) in Group A, B and C, respectively. After intravenous midazolam, as depicted in *Figure 2*, mYPAS in Group A and Group B gradually decreased from baseline value to 33.3 (IQR, 28.3–36.7) and 28.3 (IQR, 23.3–41.7) in 10 min, then 28.3 (IQR, 28.3–32.1) and 28.3 (IQR, 23.3–33.3) in 20 min, respectively. Afterward, mYPAS in both groups stabilized within 30 for the rest of the observation time.

As illustrated in *Table 2*, intravenous midazolam 0.05 mg/kg shortened the sedation onset time from 7.0±3.9 min in patients with midazolam 0.03 mg/kg to 6.0±2.4 min (P=0.025).

Parental separation

PSAS score analysis showed a total of 94 and 96 children in Group A and Group B showed satisfactory separation, accounting for 90.3% and 92.3% of the total number of children, respectively. No significant differences were found between the two midazolam groups (P=0.999). In comparison, only 80.8% (84 cases) of children in the control group received 1 or 2 points for PSAS.

Mask acceptance

Most children received satisfactory mask acceptance in Group A and Group B, with median MAS scores with 1 (IQR, 1–2) and 1 (IQR, 1–1), respectively. Although no difference was detected between the two midazolam groups (P=0.084), Group B exhibited better scores than the placebo group (P=0.010).

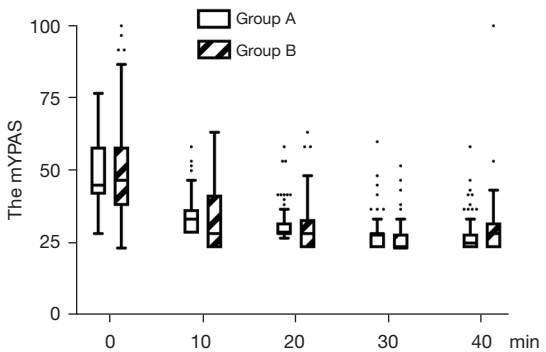

Figure 2 Box and whiskers plots of the mYPAS after 10, 20, 30, and 40 min in patients treated with 0.03 mg/kg midazolam (Group A) and 0.05 mg/kg midazolam (Group B). mYPAS, modified Yale preoperative anxiety scale.

Postoperative outcomes

None of the patients exhibited SpO_2 value lower than 95% during the perioperative period. Hemodynamic data including HR, SpO_2, and MBP during the observation period were not significantly different among the three groups (P>0.05).

In the PACU, most children were extubated at the similar time among three groups with the extubation time of 35.9±9.4, 37.1±8.6, and 37.8±10.1 min in Group A, B and C, respectively. However, children in Group B stayed longer (50.7±16.7 min) than those in Group A (46.7±10.5 min, P=0.043) and Group C (47.1±12.7 min, P=0.040). Two children in Group B and three children in Group C experienced agitation after extubation, one patient in Group A received remedial sedative medication, and two patients required airway device assisted ventilation after extubation.

Discussion

In this current randomized controlled trial, we compared two doses of intravenous midazolam administration (0.05 and 0.03 mg/kg) for premedication in pediatric patients undergoing tonsillectomy. The study demonstrated that both doses resulted in alleviation of preoperative anxiety,

Table 2 Premedication effects and postoperative outcomes

Variables	Group A (n=104)	Group B (n=104)	Group C (n=104)
Sedation onset (min)	7.0±3.9#	6.0±2.4	NA
Satisfactory separation	94 (90.3)*	96 (92.3)*	84 (80.8)
PSAS	1 [1–1]*	1 [1–1]*	1 [1–2]
MAS	1 [1–2]	1 [1–1]*	1 [1–2]
Extubation time (min)	35.9±9.4	37.1±8.6	37.8±10.1
PACU time (min)	46.7±10.5#	50.7±16.7*	47.1±12.7
PACU events	1	4	3

Data are shown as mean ± standard deviation, number (percentage) or median [interquartile range]. Time of sedation onset, rate of satisfactory separation from parents, rate of satisfactory mask acceptance, time of extubation, and duration in PACU. Group A, 0.03 mg/kg midazolam; Group B, 0.05 mg/kg midazolam; Group C, saline control. *, P<0.01, compared with group C; #, P<0.01, compared with group B; NA, not applicable. PSAS, parental separation anxiety scale; MAS, mask acceptance score; PACU, post anesthesia care unit.

ease of parental separation, and satisfactory mask induction acceptance. The higher dose of 0.05 mg/kg was associated with faster onset of sedation and longer emergence time.

For most individuals experiencing surgery, especially pediatric patients, the preoperative period is expected to be stressful. Sedative premedication helps children accept breathing masks and facilitates anesthesia induction by reducing preoperative anxiety, easing separation from parents, and minimizing emotional stress (10). Midazolam is commonly used as a premedication sedative for preoperative imaging, dentistry, orthopedic surgery, and invasive examinations due to its distinct pharmacological properties (14-16). In this study, both experimental doses showed similar sedation effects, allows for satisfactory proportion of successful parental separation and mask induction. Patients who were not labeled as satisfactory separation received remediation, mainly intravenous propofol or inhalation induction, to facilitate the separation. The remediation rate was 9.7% and 7.7% in two midazolam groups, which showed no statistically significant difference between the two groups.

The range of midazolam dosing may vary in diverse clinical situations. Theoretically, high doses do speed up the onset of action. Intravenous administration of midazolam has been reported to be with an onset of 2–3 min (17). In our study, high dose of intravenous administration shortened the onset time by around 1 minute, which is sufficient to reduce crying noise and speed up turnaround for a bustling anesthesia preparation room.

On the other hand, dose-dependent adverse effects and quality of postoperative awakening are also issues for the anesthesiologist to consider. Children who received higher doses of oral midazolam were reported to have better sedation, co-operation, and parent satisfaction scores, although adverse events of nausea and drowsiness were higher. A previous study showed that midazolam did not prolong the time to awakening or affect the incidence of postoperative agitation even when used postoperatively (18). In our study, midazolam was used as a preoperative medication, and did not affect the time to extubation, although the high-dose midazolam group stayed longer in the awakening room, yet there was only a statistical difference of less than five minutes. Consist with our results, premedication with midazolam (0.54 mg/kg) was not accompanied by a delayed emergence or discharge or an increased prevalence of complications after tonsil adenoids surgery in patients with OSA (17). Other side effects such as hypoxia, respiratory depression, airway obstruction, and apnea have been documented in fewer than 1% of pediatric patients and are considered to be dose-dependent. In addition, paradoxical effects such as uncontrollable screaming and delirium have been demonstrated in less than 15% of children who have received midazolam (19). In our trial, the children treated with premedication appeared to experience rare and similar adverse events in PACU, including agitation after extubation, remedial sedative or analgesic medication, and airway device assisted ventilation.

The current study has certain limitations that need to be addressed. First, the temperament of the children as well as parental demographic, psychological, and other factors that can influence postoperative anxiety were not evaluated. Second, in the absence of a validated scale, we employed the mYPAS in the Chinese version, which is not validated for preoperative anxiety in children. Moreover, anxiety was only assessed preoperatively. Long-term status needs to be evaluated postoperatively in future experiment (9).

Conclusions

In summary, premedication with intravenous administration of 0.05 or 0.03 mg/kg midazolam can produce similar effects on sedation status, satisfactory parental separation, and allow acceptance of breathing mask induction for anesthesia, while a single dose of 0.05 mg/kg is aligned with rapid onset and slightly extension of the emergence time.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-161/rc).

Trial Protocol: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-161/tp

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-161/dss

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-161/coif). JJ reports that the conduct of the study and publication of the manuscript was supported by the Shanghai Committee of Science and Technology, with an award (No. 21Y11900400). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by the Institutional Review Board and Ethics Committee of the Eye and ENT Hospital, Fudan University (No. 20180341). All participants and/or their parents or legal guardians provided written informed consent before participation.

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