Original Article

Intranasal esketamine versus esketamine-dexmedetomidine combination for premedication in pediatric patients undergoing strabismus surgery: a randomized controlled trial

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Background: Preoperative fear and anxiety are prevalent in children undergoing surgery. The combination of esketamine and dexmedetomidine has been proposed as a promising premedication for enhancing preoperative sedation and analgesia. This study compared the premedication efficacy of intranasal esketamine alone and esketamine-dexmedetomidine combination in pediatric patients undergoing strabismus surgery.

Methods: One hundred and eighty preschool children aged 2–6 years scheduled for strabismus surgery were enrolled and randomly assigned to one of the three groups: intranasal premedication with esketamine 2 mg/kg (Group K), esketamine 1 mg/kg and dexmedetomidine 1 μg/kg (Group KD1), or esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg (Group KD2). The primary outcome was the level of sedation following the intervention, as measured by the modified Yale preoperative anxiety scale (mYPAS) and sedation scale (SS). Secondary outcomes included onset time of sedation, the successful rate of peripheral intravenous cannulation, parental separation anxiety scale (PSAS), mask acceptance scale (MAS), wake-up time, duration of stay in the post-anesthesia care unit (PACU), and premedication-related adverse effects.

Results: After premedication, the mYPAS score gradually decreased in the three groups, with lower values in Group K than in Group KD1 and Group KD2 patients in 1, 5, and 10 min. SS in Group KD1 and Group KD2 steadily increased until 40 min after premedication, while SS in Group K increased in the first 5 min after premedication and maintained consistent levels during the remaining time. Sedation onset was substantially faster in Group K patients (11.4±7.8 min) than Group KD1 (18.1±7.5 min, P=0.006) and Group KD2 (18.4±6.8 min, P<0.001). PSAS, separation status, the successful rate of peripheral intravenous cannulation, and MAS were comparable among groups. There was no significant difference in terms of emergence time or duration of stay in the PACU among groups. More gastrointestinal events were observed in Group K (P<0.001).

Conclusions: Intranasal premedication with 2 mg/kg esketamine produced a more rapid onset of sedation accompanied by more gastrointestinal reactions compared with a combination of esketamine and dexmedetomidine.

Trial Registration: ClinicalTrials.gov identifier: NCT04757675.

Keywords: Premedication; esketamine; dexmedetomidine; sedation

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Introduction

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 (1). 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 intranasal administration of dexmedetomidine or esketamine being one of the more commonly investigated approaches (2-4).

Dexmedetomidine premedication has been proven in several trials to offer adequate preoperative sedation, minimize parental separation anxiety, increase the acceptability of induction with facemask, and reduce the incidence of emerging agitation. However, attempts at intravenous cannulation or inhalation induction with mask have been reported to disturb sleeping children, making anesthetic installation difficult. Esketamine provides a more potent analgesic and sedative effect in children than ketamine, with the additional benefit of attenuating dexmedetomidine-induced bradycardia and hypotension and accelerating the sedation onset without respiratory depression (5-7).

We believe that esketamine might be a suitable adjunct to dexmedetomidine as both medications have complementary sedation effects. Therefore, the goal of this study was to assess and compare the effectiveness of intranasal esketamine alone versus intranasal esketamine-dexmedetomidine combination as a premedication in preschool patients undergoing strabismus surgery. We present this article in accordance with the CONSORT reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-45/rc).

Highlight box

Key findings

- The use of a high dose of intranasal premedication (2 mg/kg esketamine) alone ensures a faster onset of sedation but is accompanied by more gastrointestinal adverse reactions.

What is known and what is new?

- Intranasal administration (esketamine and/or dexmedetomidine) is a common method for pediatric premedication to achieve sedation and reduce anxiety before surgery.
- This study highlights the efficacy of intranasal esketamine alone versus in combination with dexmedetomidine. Esketamine alone provides a faster onset of sedation but with more gastrointestinal side effects.

What is the implication, and what should change now?

- While intranasal esketamine at 2 mg/kg offers rapid sedation onset, its increased gastrointestinal side effects may limit its use. Clinicians should weigh the benefits of rapid sedation onset against the risk of gastrointestinal events when choosing premedication for pediatric patients.

Methods

Study participants

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). 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 (IRB approval number 2020130). The study was registered at http://ClinicalTrials.gov (NCT04757675, registrated on 17/02/2021). After being informed about the study's aim and protocol, each participant's parents or legal guardians provided written informed consent for participation.

During the study period from March 2021 to July 2021, 190 children aged 2–6 years, with American Society of Anesthesiologists (ASA) physical status I–II, who were scheduled for elective strabismus surgery under general anesthesia were recruited. Exclusion criteria included pediatric patients with emergent surgery; ASA physical status of III or IV; allergic history of dexmedetomidine, esketamine, or ketamine; intranasal pathology or running nose; upper airway infection; congenital heart disease or infective cardiomyopathy; epilepsy or central nervous system developmental abnormalities; and parents' refusal.

Consecutive patients were randomly assigned to the following three groups according to premedication with esketamine (Aisi®, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, China) and/or dexmedetomidine (Youbituo®, Yangtze River Pharmaceutical Group, Taizhou, China): intranasal esketamine 2 mg/kg (Group K), a combination of esketamine 1 mg/kg and dexmedetomidine 1 μg/kg (Group KD1), or a combination of esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg (Group KD2). A computer-generated randomization table was used to randomize in a 1:1 ratio. An independent nurse staff team not involved in the trial recruited, screened, and performed the randomization and drug preparation in 1-mL syringes.

Table 1 Scales and scores system to evaluate sedation and separation status

Scales	Behavior to corresponding scores
SS	
1	Agitated, clinging to parents, crying
2	Alert, awake may whimper not crying
3	Calm, sitting or lying comfortably with eyes open
4	Drowsy, lying comfortably with eyes closed, responds to minor stimulus
5	Asleep, no response to minor stimulus
ESS	
1	Calm
2	Apprehensive, not smiling, tentative behavior, withdrawn
3	Crying
4	Thrashing, crying with movements of the arms and legs, resisting
PSAS	
1	Easy to separate
2	Sobbing but easy to cease
3	Crying loudly and difficult to stop but without holding the parents and not letting them go
4	Crying loudly and holding the parents and not willing to let them go
MAS	
1	Not afraid, cooperative, 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

SS, sedation scale; ESS, emotional state score; PSAS, parental separation anxiety scale; MAS, mask acceptance scale.

The medication in identical syringe was evenly sprayed into both nostrils. By sealing the group assignments in opaque envelopes that were sequentially numbered, the parents or legal guardians, the involved anesthesiologist and surgeons, and the data collection technicians were all blinded. The heart rate (HR) and pulse oxygen saturation (SpO_2) were monitored and recorded before intranasal administration, as well as 10, 20, and 30 min after drug administration.

Anesthesia administration

Before premedication, continuous monitoring with non-invasive blood pressure, electrocardiograph, and pulse oximetry were conducted. All patients were observed for 40 min after receiving intranasal premedication before being transferred into the operating room (OR) on a transferring bed. General anesthesia was initiated with 3 mg/kg propofol, 2 μg/kg fentanyl, 0.6 mg/kg rocuronium, and then ventilated with a laryngeal mask airway (LMA) during surgery. The surgical procedures were performed by three operators who were not aware of the children's premedication status. Following the completion of the surgery, the patients were transported to the post-anesthesia care unit (PACU), where an independent anesthesiologist was responsible for monitoring and medical intervention of the children. The children were transferred to the ward when they met the discharge criteria according to the consciousness, mobility, and physiological parameters.

Outcome assessment

The primary outcome was the level of sedation after receiving the research medication. The modified Yale preoperative anxiety scale (mYPAS) (8) and the sedation scale (SS) (9) were used to assess the level of sedation at 10, 20, 30, and 40 min following intranasal premedication (*Table 1*). All assessments were conducted by an experienced anesthetic nurse who works exclusively in the preoperative anesthesia preparation room. 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. Higher scores on this scale indicate a higher level of anxiety. A score of more than or equal to 30 indicates the existence of severe anxiety (8).

Secondary outcomes included 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 was determined as the duration from premedication administration until the time the child complained of dizziness or drowsy, or the SS score reached 3 points (10). A trained nurse anesthetist, masked to the

group assignment, performed venous cannulation with at least three years of clinical experience. Regardless of whether the vein was cannulated on the first attempt or not, successful venous cannulation was defined as an emotional state score (ESS, *Table 1*) of no more than 2 points at the attempted cannulation. Parental separation anxiety was assessed using the parental separation anxiety scale (PSAS, *Table 1*) during the transfer from the premedication center to OR according to four levels. A satisfactory sedative effect at separation was considered as PSAS was no more than 2 points. The mask compliance was graded on a four-point scale according to the mask acceptance scale (MAS, *Table 1*) (11). The percentage of children with "satisfactory" scores of parental separation anxiety was recorded separately in each group. The HR, mean blood pressure, sedation level, and medication-related adverse effects were observed and recorded every 5 min. An anesthesia nurse who was unaware of the administered drug and not involved directly in the patients' care rated and recorded study data.

Sample size calculation and statistical analyses

The sample size was calculated based on sedation level (SS score) in our previous study, which was equivalent to 1 (0.25) at 30 min after intranasal dexmedetomidine $2.5 \cdot \mu g \cdot kg^{-1}$ (12). Therefore, the required sample size to detect a difference of 0.5 in the sedation score was predicted to be at least 45 patients in each group by considering 80% power and 95% confidence interval. We enrolled 190 patients in all, anticipating that not all patients would be evaluated appropriately. 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. Data normality of distribution and homogeneity of variances were tested using Shapiro-Wilk's and Levene's tests, respectively. Analysis of variance (ANOVA) was used to compare three groups regarding demographic characteristics and hemodynamic parameters at different times following the operation. The Kruskal-Wallis test was performed to compare three groups based on sedation status, mask acceptability, and ease of separation. Furthermore, ANOVA for repeated measurements was utilized to assess the fluctuation of hemodynamic variables at various time points. The summarized results were illustrated in tables or figures. All data analysis were processed with SPSS 25.0 software package (IBM SPSS Inc., Armonk, USA), and all test of statistical significance was inferred at two-tailed $P<0.05$.

Results

Patients recruitment

During the trial period, a total of 190 children were screened for eligibility. Six parents declined to participate, and four children were found to have a running nose on the day of surgery (*Figure 1*). As a result, 180 patients were enrolled and randomly assigned to one of the three groups. Six patients in Group K were lost to follow-up. Four surgeries were canceled, four children were lost to follow-up, and three children were withdrawn because they resisted the intranasal premedication in Group KD1. Six patients were lost to follow-up, one surgery was canceled, three children were intravenously cannulated in the ward rather than anesthesia preparation room in Group KD2. Finally, 153 pediatric patients were eligible for the final analysis. Demographic characteristics, e.g., sex, age, weight, height, body mass index, ASA classification, anesthesia duration, and surgeon assignment, were comparable among groups (*Table 2*).

Primary outcome

The sedation status assessed by mYPAS and SS is illustrated in *Figure 2*. Baseline mYPAS was comparable among groups, with median [quartile] of 46.7 [32.5–50], 46.7 [46.7–60.4], and 51.7 [46.7–64.5] in Group K, Group KD1, and Group KD2, respectively. At 1, 5, and 10 min after the premedication, the mYPAS was lower in Group K compared with Group KD1 and Group KD2. Afterward, the mYPAS was found no significant difference among the three groups at 20, 30, and 40 min after premedication. Similarly, no significant differences were found regarding SS preoperatively {median [quartile]: 2 [2–3], 2 [2–2.25], and 2 [2–2] in Group K, Group KD1, and Group KD2, respectively}. At 1 min after premedication, SS in Group K {3 [2–3]} was found to be higher than those in Group KD1 {2 [1–2], $P<0.001$} and Group KD2 {2 [1.5–2], $P<0.001$}. No significant differences were detected among the three groups at 5, 10, and 20 min after premedication. However, the SS value at 30 and 40 min after premedication in Group KD1 {4 [3–5], 5 [3–5]} and Group KD2 {4 [4–5], 5 [5–5]} exceeds the values in Group K {3 [2.75–3], 3 [2–3]}.

Secondary outcomes

All data met the assumptions of normality ($P=0.76$). HR changes after premedication are illustrated in *Figure 3*. HR

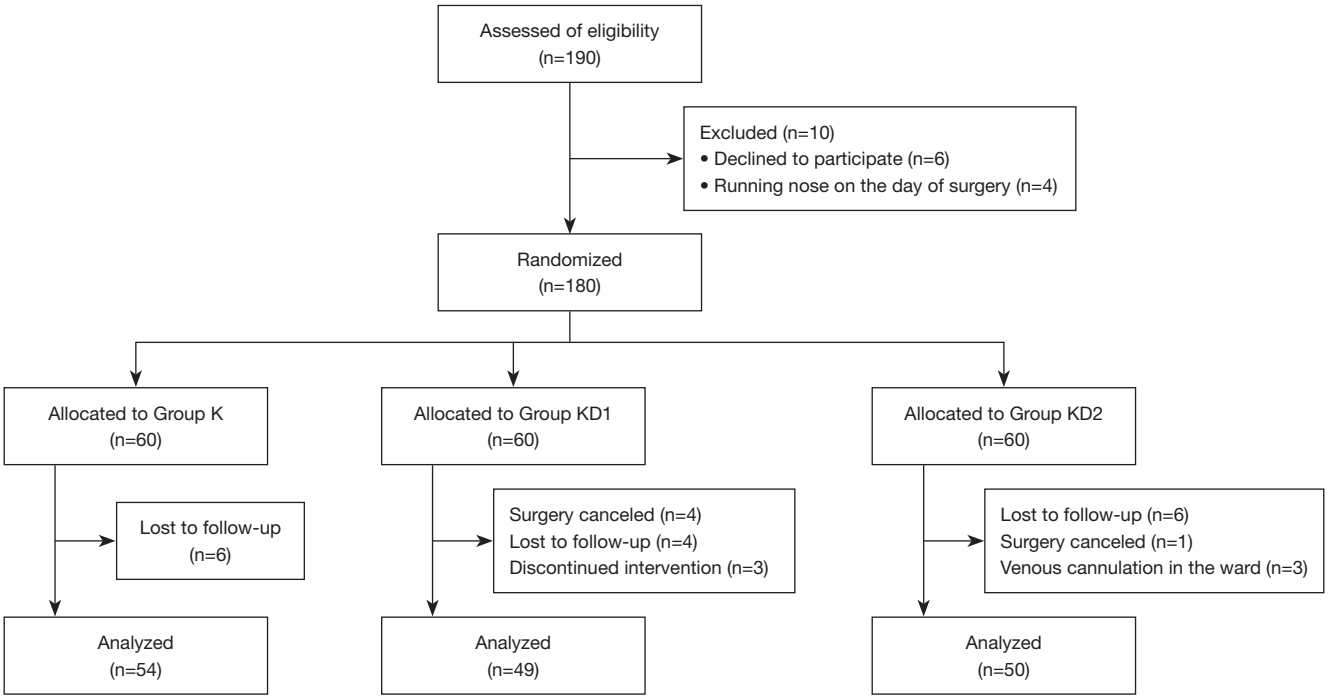

Figure 1 Consort flow diagram. Group K, intranasal premedication with esketamine 2 mg/kg; Group KD1, intranasal premedication with esketamine 1 mg/kg and dexmedetomidine 1 μg/kg; Group KD2, intranasal premedication with esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg.

Table 2 Demographic characteristics

Demographic characteristics	Group K (n=54)	Group KD1 (n=49)	Group KD2 (n=50)	P value
Sex (male/female)	25/29	25/24	16/34	0.14
Age (years)	4.9±1.7	4.4±1.6	4.5±1.4	0.18
Weight (kg)	17.9±4.2	16.7±3.4	16.3±3.1	0.07
Height (cm)	106.1±13.5	105.3±10.5	102.7±12.6	0.34
Body mass index (kg/m^2)	15.7±1.6	15.6±1.7	15.3±2.1	0.91
ASA physical status (I/II)	51/3	44/5	45/5	0.93
Anesthesia duration (min)	42.4±14.2	46.9±18.6	47.0±18.1	0.27
Operator (1/2/3)	34/12/8	40/5/4	38/5/7	0.20

The values are presented as the mean ± SD or the number of patients. Group K, intranasal premedication with esketamine 2 mg/kg; Group KD1, intranasal premedication with esketamine 1 mg/kg and dexmedetomidine 1 μg/kg; Group KD2, intranasal premedication with esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg. The P values were calculated by the Mann-Whitney *U* test, Chi-squared test, or Fisher exact test. ASA, American Society of Anesthesiologists; SD, standard deviation.

in Group K (110±15 beats per minute, bpm) was higher than those in Group KD1 (100±14 bpm, P=0.01) and Group KD2 (103±9 bpm, P=0.03). Afterwards, significant differences were found only between Group K and Group KD2 in 10 min (109±13 *vs.* 100±10 bpm, P=0.002), 20 min (109±12 *vs.* 99±10 bpm, P<0.001) and 30 min (106±15 *vs.* 95±9 bpm, P=0.006) after premedication, respectively.

As presented in *Table 3*, intranasal ketamine 2 mg/kg

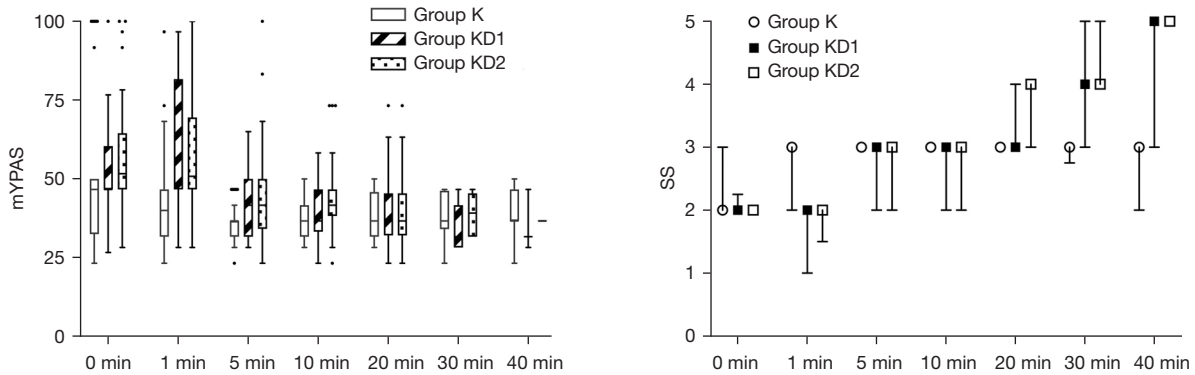

Figure 2 Box and whisker (median with interquartile range) plots of the mYPAS and SS after the intervention. Group K, intranasal premedication with esketamine 2 mg/kg; Group KD1, intranasal premedication with esketamine 1 mg/kg and dexmedetomidine 1 μg/kg; Group KD2, intranasal premedication with esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg. mYPAS, modified Yale preoperative anxiety scale; SS, sedation scale.

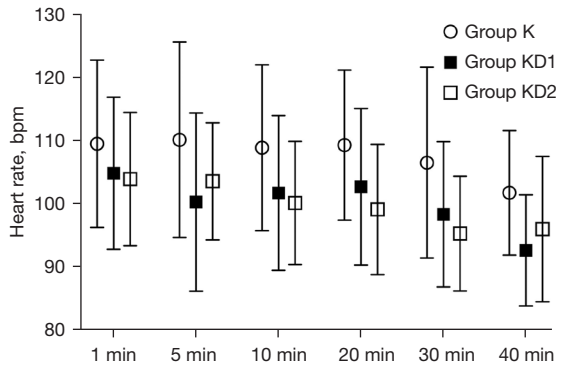

Figure 3 Heart rate changes after receiving intranasal premedication. Heart rates decreased significantly from baseline at 10, 20, 30, and 40 min in Group K, Group KD1, and Group KD2. Group K, intranasal premedication with esketamine 2 mg/kg; Group KD1, intranasal premedication with esketamine 1 mg/kg and dexmedetomidine 1 μg/kg; Group KD2, intranasal premedication with esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg.

shortened the sedation onset time to 11.4±7.8 min in Group K, compared with 18.1±7.5 min (P=0.006) in Group KD1 and 18.4±6.8 min (P<0.001) in Group KD2. The proportions of successful venous cannulation were similar among the three groups, approximately 70.3%, 71.4%, and 82.0%, respectively (P=0.33). When separated from parents, most children showed satisfactory PSAS with a median of 1 and 25–75% percentile of 1–2 in all groups. The number of patients (percentage) with satisfactory separation was 37 (68.5%), 37 (75.5%), and 40 (80%) in Group K, Group KD1, and Group KD2, respectively (P=0.34). LMA removal time (P=0.38) and the duration in PACU (P=0.32) showed no significant difference among the three groups.

Premedication-associated adverse events

Detailed information regarding adverse events is presented in *Table 4*. A significantly higher number and percentage of patients (14, 25.9%) in Group K developed gastrointestinal events, i.e., nausea, vomiting, hiccup, and abdominal pain, compared to those in Group KD1 (3, 6.1%, P<0.001) and Group KD2 (1, 2.0%, P<0.001). The occurrence of other complications related to premedication, i.e., increased glandular secretion, nystagmus, abnormal behavior, irritability, dizziness, was identified as no statistically significant difference among groups. The patients treated with three premedication approaches appeared to experience similar adverse events in PACU, including agitation after LMA removal, remedial sedative or analgesic medication, airway device assisted ventilation, and massive secretions.

Discussion

Esketamine, known as the N-methyl-D-aspartate (NMDA) receptor antagonist, has anesthetic, analgesic, and sympathomimetic characteristics that are 2–3 times more effective than ketamine, and is believed to be associated with rapid recovery, less cardiorespiratory inhibition, and fewer psychotomimetic adverse effects. As a result, it could be an ideal premedication for a preoperative anxiolytic. However, there are still concerns about causing psychiatric symptoms, increased secretion, or other unexpected events

Table 3 Secondary outcomes

Secondary outcomes	Group K (n=54)	Group KD1 (n=49)	Group KD2 (n=50)
Sedation onset (min)	11.4±7.8	18.1±7.5[#]	18.4±6.8*
Successful intravenous cannulation	38 (70.3)	35 (71.4)	41 (82.0)
PSAS	1 [1]	1 [1]	1 [1]
Satisfactory separation	37 (68.5)	37 (75.5)	40 (80.0)
MAS	1 [1]	1 [0.25]	1 [1]
LMA removal time (min)	36.9±10.9	34.2±7.0	35.6±6.6
PACU time (min)	58.7±18.6	54.5±12.8	54.4±13.5

Values are presented as mean ± standard deviation, median [interquartile range], or number (%). Group K, intranasal premedication with esketamine 2 mg/kg; Group KD1, intranasal premedication with esketamine 1 mg/kg and dexmedetomidine 1 μg/kg; Group KD2, intranasal premedication with esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg. *, P<0.001, compared with Group K; [#], P=0.006, compared with Group K. PSAS, parental separation anxiety scale; MAS, mask acceptance scale; LMA, laryngeal mask airway; PACU, post-anesthesia care unit.

Table 4 Premedication-associated adverse events

Adverse events	Group K (n=54)	Group KD1 (n=49)	Group KD2 (n=50)	P value
Gastrointestinal events	14	3	1	<0.001
Glandular events	6	1	5	0.18
Nystagmus	4	1	2	0.42
Abnormal behavior	3	3	3	0.99
Irritability	6	4	1	0.19
Dizziness	9	6	2	0.12
PACU events	6	4	5	0.88

Group K, intranasal premedication with esketamine 2 mg/kg; Group KD1, intranasal premedication with esketamine 1 mg/kg and dexmedetomidine 1 μg/kg; Group KD2, intranasal premedication with esketamine 0.5 mg/kg and dexmedetomidine 2 μg/kg. Gastrointestinal events included nausea, vomiting, hiccup, and abdominal pain; Glandular events included lachrymation, salivation, running nose, and sweating; Abnormal behavior included talkative behavior, heteronomous head shaking, and face expression distortion; PACU events included agitation after laryngeal mask removal, remedial sedative or analgesic medication, airway device assisted ventilation and massive secretions. PACU, post-anesthesia care unit.

for preoperative use (13). Dexmedetomidine, α-2 adrenergic receptors agonists, produces sedation and decrease of blood pressure and HR by activating inhibitory GABAergic interneurons in the brainstem. Dexmedetomidine has been proved to be efficient in many clinical studies for premedication (14,15). Theoretically, when administered in conjunction with esketamine, dexmedetomidine can reduce psychotic effects and neuronal hyperactivity (4). The goal of this study was to compare the sedation effects of esketamine and esketamine-dexmedetomidine combination intranasally used for premedication.

So far, no single medication can solve all the issues that pediatric patients may encounter preoperatively, such as parent-child separation, pain during the vein cannulation, and cooperation with mask oxygenation. Thus, a growing number of clinical studies or animal experiments using various drug combinations have been conducted to explore the ideal premedication regimen (16,17). According to a recent trial, the combination of oral midazolam and intranasal esketamine provides the advantages of a quicker onset, less behavioral abnormalities, and faster recovery. When compared to intranasal midazolam 0.2 mg/kg, premedication with intranasal 2 g/kg dexmedetomidine and oral 3 mg/kg ketamine is a faster and more effective option for children undergoing dental rehabilitation (18). In our study design, the doses of both drugs used in

combination were reduced to varying degrees, with the aim of achieving the same sedative effect while reducing adverse reactions. According to our findings, the combined use of dexmedetomidine and esketamine showed the similar success rates for intravenous cannulation and compliance for mask induction as high-dose esketamine alone, with relatively slow-acting sedative effect.

One crucial consideration when it comes to preoperative medicine is whether it impacts postoperative recovery and adverse reactions. In an *in vivo* research, only 0.25 mg/kg dexmedetomidine was found to be sufficient to reduce esketamine-related psychotomimetic adverse reactions in Kunming mice without extending recovery time (7).

In adult patients, low-dose esketamine administered for sedation has no influence on wake-up time, surgeon and patients' satisfaction, adverse effects, and cardiovascular or respiratory adverse events (19). Consistent with our results, both the combination and single premedication were acceptable considering the quality of postoperative emergence. HR variability is one of the adverse effects of dexmedetomidine and requires special attention especially for pediatric patients (20). In our study, esketamine did not significantly affect the HR of the pediatric patients, and only dexmedetomidine up to 2 μg/kg in the combination group presented a statistically significant decrease in HR, which was also considered to be within the acceptable range. Although high doses of esketamine significantly accelerated the onset of action, the associated adverse effects, particularly gastrointestinal discomfort, presented as nausea, vomiting, hiccup, and abdominal pain, added to the anxiety of the children and parents.

Conclusions

In conclusion, premedication with intranasal esketamine and a combination of small-dose dexmedetomidine and esketamine produces similar levels of sedation and natural parental separation, while 2 mg/kg esketamine resulted in a rapid onset and more gastrointestinal events.

Acknowledgments

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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-24-45/rc

Trial Protocol: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-45/tp

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-45/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-45/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-45/coif). The 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). 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 (IRB approval number 2020130). The study was registered at http://ClinicalTrials.gov (NCT04757675, registrated on 17/02/2021). After being informed about the study's aim and protocol, each participant's parents or legal guardians provided written informed consent for participation.

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