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CLINICAL TRIAL REPORT

# Ketamine Enhances Intranasal Dexmedetomidine-Induced Sedation in Children: A Randomized, Double-Blind Trial

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**Purpose:** To compare the efficacy of intranasal dexmedetomidine and dexmedetomidine-ketamine premedication in preschool children undergoing tonsillectomy.

**Patients and Methods:** We enrolled 66 children with American Society of Anesthesiologists physical status I or II, aged 3–7 years undergoing tonsillectomy. Patients were randomly allocated to receive intranasal premedication with either dexmedetomidine 2 μg $kg^{-1}$ (Group D) or dexmedetomidine 2 μg $kg^{-1}$ and ketamine 2 mg $kg^{-1}$ (Group DK). The primary outcome was the sedation level assessed by the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) 30 min after intervention. The minimal clinically relevant difference in the MOAA/S score was 0.5. Secondary outcomes included sedation onset time, parental separation anxiety, acceptance of mask induction, emergence time, emergence delirium, postoperative pain intensity, length of stay in the post-anesthesia care unit (PACU), and adverse effects.

**Results:** At 30 min after premedication, the MOAA/S score was lower in Group DK than in Group D patients (median: 1.0, interquartile range [IQR]: 1.0–2.0 vs median: 3.0, IQR: 2.0–3.0; $P<0.001$), with a median difference of 1.0 (95% confidence interval [CI]: 1.0–2.0, $P<0.001$). Patients in Group DK showed considerably faster onset of sedation (15 min, 95% CI: 14.2–15.8 min) than Group D (24 min, 95% CI: 23.2–24.8 min), with a median difference of 8.0 min (95% CI: 7.0–9.0 min, $P<0.001$). Both parental separation and facemask acceptance scores were lower in Group DK than in Group D patients ($P=0.012$ and $P=0.001$, respectively). There was no significant difference in emergence time, incidence of emergence delirium, postoperative pain scores, and length of stay in the PACU between the two groups.

**Conclusion:** Intranasal premedication with a combination of dexmedetomidine and ketamine produced better sedation for pediatric tonsillectomy than dexmedetomidine alone.

**Keywords:** preoperative sedation, mask induction, pediatric anesthesia

## Introduction

Preoperative anxiety is common in pediatric patients undergoing surgery. Anxiety is associated with adverse outcomes via elevation of stress markers, promoting fluctuations in hemodynamics, and negatively impacting postoperative recovery.[1,2] To alleviate preoperative anxiety and achieve a smooth induction of inhalation anesthesia, a variety of pharmacological and nonpharmacological methods have been proposed as preoperative anxiolytics to minimize the distress of children in the operating room.[3] The ideal preoperative medication should be natural to accept, fast

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in onset and offset, and reliable in achieving a targeted sedation level without any adverse effects.

Given its favorable sedative and anxiolytic properties with minimal respiratory depression, there is growing interest in the use of dexmedetomidine, a highly selective alpha-2 adrenergic agonist, for pediatric premedication.[4,5] Several studies have shown that dexmedetomidine premedication provides satisfactory preoperative sedation, alleviates parental separation anxiety, promotes the acceptance of facemask induction, and decreases the incidence of emergence delirium.[6,7] When used as premedication in pediatric patients, intranasal dexmedetomidine has been shown to confer an advantage over oral midazolam (the most commonly used premedication).[8] Nonetheless, attempts at mask inhalation induction or intravenous cannulation have been reported to arouse children from sedation and result in challenges for the installation of anesthesia.[9] Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist with sedative, analgesic, anesthetic, immobility, and amnesic properties.[10] Ketamine may attenuate dexmedetomidine-induced bradycardia and hypotension, and accelerate the onset of sedation with no respiratory depression.[11]

We suggest that ketamine may represent a suitable auxiliary medicine of dexmedetomidine because both exhibit complementary pharmacological effects. Therefore, this study aimed to evaluate and compare the efficacy of the combination of intranasal dexmedetomidine and intranasal ketamine-dexmedetomidine as a premedication administered 30 min before induction of anesthesia in children undergoing tonsillectomy.

# Patients and Methods

## Enrolment and Eligibility

The Biological-Medical Ethical Committee of Fujian Provincial Hospital approved this randomized, double-blind comparative study (Identifier: K2016-02-11). The study followed the regulations of the Helsinki Declaration and was prospectively registered in the Australian New Zealand Clinical Trials Registry (Identifier: ACTRN12616001522404). Written informed consent was obtained from parents or legal guardians before patient participation in the study. We conducted this trial according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement at Fujian Provincial Hospital, China, between January 2017 and October 2017.[12]

## Randomization and Blinding

We enrolled pediatric patients aged 3–7 years, with American Society of Anesthesiologists (ASA) physical status I or II, who were scheduled for elective tonsillectomy. Patients with acute upper respiratory infection, a history of asthma, known allergy to dexmedetomidine or ketamine, cardiac dysrhythmias, or a history of psychiatric disorder were excluded. Sixty-six patients were randomly allocated to receive intranasal premedication with either dexmedetomidine 2 μg $kg^{-1}$ (Group D) or dexmedetomidine 2 μg $kg^{-1}$ and ketamine 2 mg $kg^{-1}$ (Group DK). Randomization was based on a 1:1 ratio using a computer-generated randomization table. An independent nurse not involved in the study recruited participants, screened, and implemented the randomization. Group allocations were concealed in sequentially-numbered, sealed opaque envelopes. Dexmedetomidine at a concentration of 100 μg $mL^{-1}$ and ketamine at a concentration of 50 mg $mL^{-1}$ were used. The study drugs were prepared without dilution in identical syringes by an independent nurse not involved in the study. The volumes of dexmedetomidine and ketamine were 0.02 mL $kg^{-1}$ and 0.04 mL $kg^{-1}$, respectively. Thus, the final amount of the intranasally administered solution was 0.06 mL $kg^{-1}$. The study drug was introduced into both nostrils equally using a nasal mucosal atomization device (MAD Nasal™, Wolfe-Tory Medical Inc., UT, USA). The patient's parents, the attending anesthesiologist, the surgeons, and data collection personnel were blinded to the group assignment.

## Standard Study Protocol

At the end of the intranasal administration of the premedication, all patients were observed for 30 min before general anesthesia was induced. Upon arrival in the operation room, all patients were subjected to the standard monitoring protocol including peripheral pulse oximetry, electrocardiography, capnography, and non-invasive blood pressure measurement. General anesthesia was induced with 5% sevoflurane in 100% oxygen at 10 L $min^{-1}$ using a Jackson Rees breathing circuit, and then an intravenous cannula was inserted. We administered sufentanil 0.5 μg $kg^{-1}$, propofol 2.0 mg $kg^{-1}$, and cisatracurium 0.1 mg $kg^{-1}$ intravenously to facilitate endotracheal intubation. All patients received infiltration of 0.2% ropivacaine into the peritonsillar fossa before the surgical procedure. Volume-controlled mechanical ventilation was used to maintain an end-tidal carbon dioxide partial pressure ($PaCO_2$) of 35–45 mmHg. Anesthesia was

maintained using sevoflurane in a 50% oxygen/air mixture. Granisetron 20 μg $kg^{-1}$ and dexamethasone 0.1 mg $kg^{-1}$ were administered 30 min before the end of surgery. The tracheal tube was extubated once the patient could resume spontaneous breathing. The patients were then transferred to the post-anesthesia care unit (PACU) for a one-hour observation in the presence of one parent.

## Outcome Assessment

The primary outcome was the sedation level at 30 min after the study drug administration. The level of sedation was evaluated at 10, 20, and 30 min after intranasal premedication using the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S).[13] Secondary outcomes included onset of sedation, parental separation anxiety, acceptance of mask induction, emergence time, emergence delirium, postoperative pain intensity, length of stay in the PACU, and adverse effects. The time of sedation onset was defined as the interval between after premedication and reaching a score of 3 on the MOAA/S. The patient's reaction to separation from the parents was recorded 30 min after premedication using a four-point Parental Separation Anxiety Scale (PSAS) as follows: 1 = easy separation, 2 = whimpers, but is easily reassured, not clinging, 3 = cries and cannot be easily reassured, but not clinging to parents, and 4 = crying and clinging to parents.[14] The acceptance of mask induction was graded using the mask acceptance scale (MAS) as follows: 1 = excellent (unafraid, cooperative, accepts mask easily), 2 = good (slight fear of mask, easily assured), 3 = fair (moderate fear of mask, not calmed with reassurance), and 4 = poor (terrified, crying, or combative).[15] Emergence time was defined as the interval from discontinuation of sevoflurane to eye-opening on verbal command. The children were assessed every 15 min during the stay in the PACU, and the maximum Pediatric Anesthesia Emergence Delirium (PAED) score was recorded. Emergence delirium was defined as a PAED score in the PACU greater than or equal to 10.[16] Propofol 1 mg $kg^{-1}$ was administered intravenously to treat emergence delirium, when necessary. Postoperative pain intensity was evaluated at 15 min intervals until the patient was discharged from the PACU using the Face, Legs, Activity, Cry, and Consolability (FLACC) scale ranging from 0 to 10.[17] If the FLACC score reached more than 3, intravenous morphine 25 μg $kg^{-1}$ was administered to rescue analgesia. The duration of stay in the PACU was defined from admission to the PACU up to the time to reach a modified Aldrete recovery score of 9.[18] Additionally, all episodes of adverse events such as bradycardia, hypotension, laryngospasm, hypoxemia, postoperative nausea and vomiting (PONV), and negative behavioral changes from premedication to postoperative 24 hours were recorded. A single trained investigator blinded to the group assignment assessed all the above outcomes.

## Sample Size and Statistical Analyses

The sample size calculation was based on the level of sedation (MOAA/S score) at 30 min after intranasal premedication. According to a previous study, the MOAA/S score at 30 min after intranasal dexmedetomidine 2 μg $kg^{-1}$ was equivalent to 2.55±0.69.[19] Therefore, with $\alpha$=0.05 and $\beta$=0.2, the sample size required to detect a difference of 0.5 in the MOAA/S score was estimated to be 30 patients per group. We enrolled a total of 66 patients, anticipating that not all patients would be fully evaluable.

All of the individual participant data were analyzed using SPSS version 25.0 (IBM SPSS Inc., Armonk, USA). One sample Kolmogorov–Smirnov test was used to investigate the normality distribution of the continuous variables. As most of our data were not normally distributed, the Mann–Whitney *U*-test was used for the analysis. Categorical variables were compared using the $\chi^2$ test or Fisher's exact test, where appropriate. The Mann–Whitney test was used to compare quantitative variables between the two groups. The *P*-value was set at 0.05 for statistical significance.

# Results

During the study period, 72 children were screened for eligibility, of which six were excluded (Figure 1). Thus, 66 patients were enrolled and randomized. One patient in Group D and two patients in Group DK were withdrawn due to protocol breach because they resisted the intranasal premedication. A total of 63 children were included in the analysis. There were no significant differences in subject characteristics (age, sex, weight, height, and ASA physical status) or clinical parameters between the two groups (Table 1).

The MOAA/S scores are presented in Figure 2. At 10 min after premedication, the MOAA/S score was lower in Group DK compared with Group D (median: 4.0, interquartile range [IQR]: 4.0–5.0 vs median: 5.0, IQR: 5.0–6.0; *P*<0.001), with a median difference of 1.0 (95% confidence interval [CI]: 1.0–1.0, *P*=0.001). At 20 min after premedication, the MOAA/S score was lower in Group DK compared

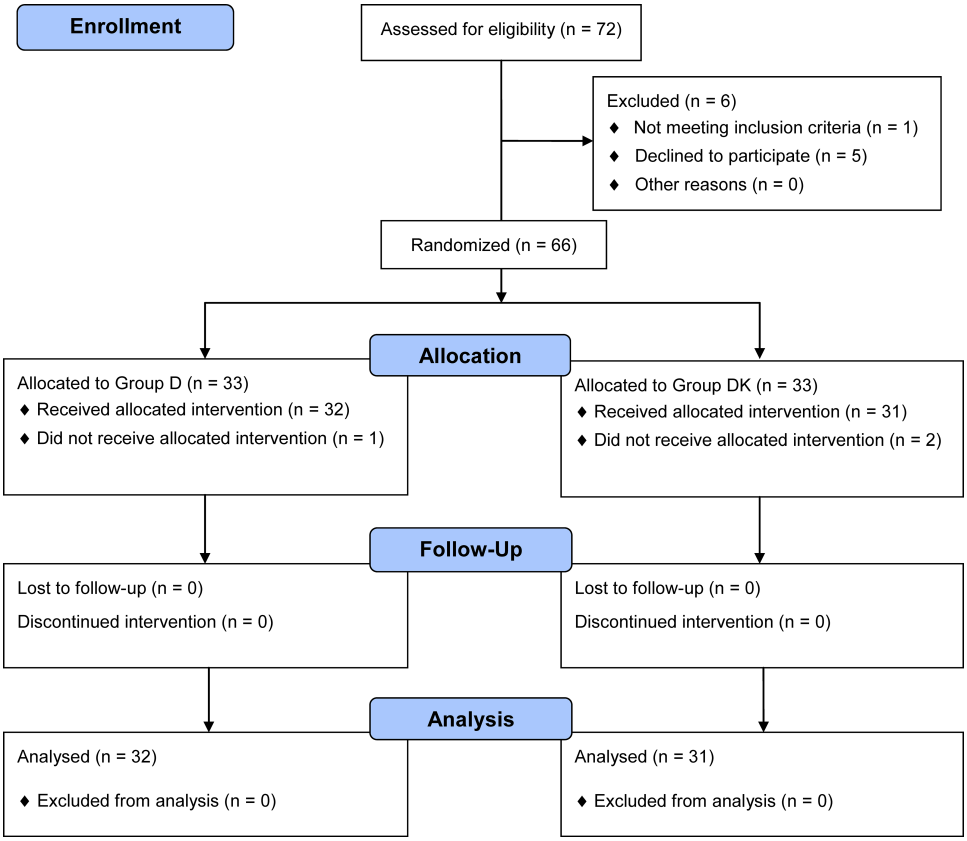


**Figure 1** Consolidated Standards of Reporting Trials (CONSORT) flow diagram illustrating the patient progress through the study.

with Group D (median: 2.0, IQR: 2.0–2.0 vs median: 3.5, IQR: 3.0–4.0; $P<0.001$), with a median difference of 1.0 (95% CI: 1.0–2.0, $P<0.001$). At 30 min after premedication, the MOAA/S score was lower in Group DK compared with Group D (median: 1.0, IQR: 1.0–2.0 vs median: 3.0, IQR: 2.0–3.0; $P<0.001$), with a median difference of 1.0 (95% CI: 1.0–2.0, $P<0.001$). As shown in Figure 3, intranasal ketamine shortened the median of sedation onset time from 24 min (95% CI: 23.2–24.8 min) in Group D to 15 min (95% CI: 14.2–15.8 min) in Group DK, with a median difference of 8.0 min (95% CI: 7.0–9.0 min, $P<0.001$).

Ease of parental separation and facemask acceptance scores are detailed in Table 2. Briefly, both PSAS and

**Table 1** Patient Demographics and Clinical Data

| | Group D, n = 32 | Group DK, n = 31 | *P*-value |
|---|---|---|---|
| Sex (male/female), n | 21/11 | 18/13 | 0.537 |
| Age, years | 5.5 ± 0.4 | 5.3 ± 0.6 | 0.141 |
| Height, cm | 112.4 ± 5.9 | 113.2 ± 6.6 | 0.646 |
| Weight, kg | 20.9 ± 2.5 | 20.3 ± 3.1 | 0.336 |
| ASA physical status (I/II), n | 32/0 | 31/0 | NS |
| Duration of anesthesia, min | 90.9 ± 5.2 | 92.4 ± 6.5 | 0.332 |
| Duration of surgery, min | 57.7 ± 4.6 | 56.6 ± 5.6 | 0.392 |

**Notes:** Data are presented as mean ± SD or number.
**Abbreviations:** ASA, American Society of Anesthesiologists; NS, no significance.

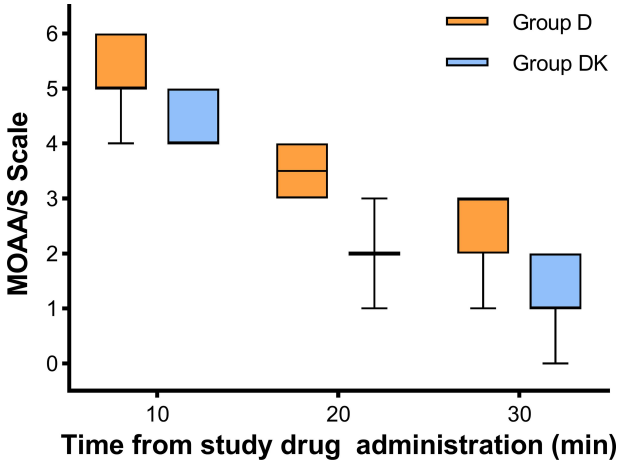


**Figure 2** Box and whiskers (min to max) plots of the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) scores after intervention. The MOAA/S scores were lower in the dexmedetomidine and ketamine-treated patients (Group DK) than patients treated with dexmedetomidine alone (Group D) at 10, 20, and 30 min after premedication (all $P<0.001$).

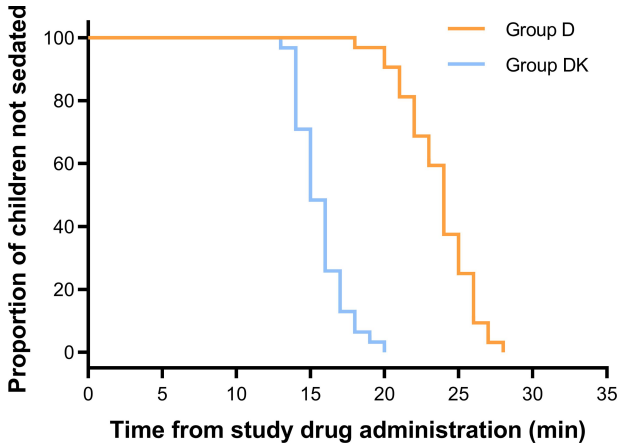


**Figure 3** Kaplan-Meier curves for the sedation onset time after premedication in minutes. The median sedation onset time in the dexmedetomidine and ketamine treated group (Group DK) (15 min, 95% CI: 14.2–15.8 min) was shorter than patients treated with dexmedetomidine alone (Group D) (24 min, 95% CI: 23.2–24.8 min), ($P$<0.001 by Log Rank test).

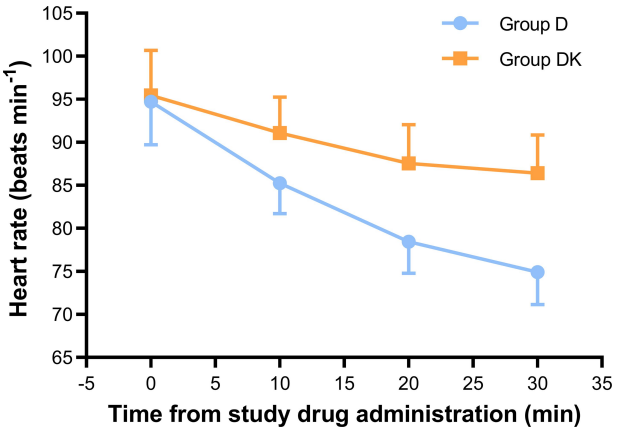


**Figure 4** Changes in heart rates after patients received intranasal premedication. Heart rates declined significantly from baseline at 10, 20, and 30 min in patients treated with dexmedetomidine alone (Group D) compared with the dexmedetomidine and ketamine treated group (Group DK) (all $P$<0.001).
**Note:** Data are represented as mean±SD.

MAS scores were lower in Group DK compared with Group D ($P$=0.012 and $P$=0.001, respectively). There were no significant between-group differences with regard to emergence time, the incidence of emergence delirium, postoperative pain score (FLACC) in the PACU, length of stay in the PACU, and the incidence of PONV (all $P$>0.05). As presented in Figure 4, heart rates declined from baseline at 10, 20, and 30 min after intranasal administration in Group D compared with Group DK (all $P$<0.001). Regarding perioperative adverse events, one patient in Group D and two patients in Group DK reported postoperative vomiting. No bradycardia, hypotension, laryngospasm, hypoxemia, or negative behavioral changes occurred in this study.

**Table 2** Secondary Outcomes During the Study

| | Group D, n=32 | Group DK, n=31 | *P*-value |
|---|---|---|---|
| Sedation onset time, min | 24.0 [22.0–25.8] | 15.0 [14.0–17.0] | < 0.001 |
| PSAS score | 1 [1–1] | 1 [1–1] | 0.012 |
| MAS score | 1 [1–2] | 1 [1–1] | 0.001 |
| Emergence time, min | 16.0 [15.0–18.0] | 17.0 [16.0–18.0] | 0.093 |
| Emergence delirium, n (%) | 2 (6.3) | 3 (9.7) | 0.672 |
| FLACC pain scale | 1 [1–2] | 1 [1–2] | 0.668 |
| Length of stay in PACU, min | 21.1±2.8 | 20.5±2.9 | 0.367 |
| PONV, n (%) | 1 (3.1) | 2 (6.5) | 0.613 |

**Notes:** Data are presented as mean ± SD, median [IQR], or number (%).
**Abbreviations:** PSAS, Parental Separation Anxiety Scale; MAS, mask acceptance scale; FLACC, the Face, Legs, Activity, Cry, and Consolability scale; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting.

## Discussion

Premedication for pediatric patients via the intranasal administration of a combination of ketamine and dexmedetomidine achieved a higher sedation score, more natural separation from parents, and smoother inhalational induction than intranasal dexmedetomidine alone, with no extension of the emergence time after sevoflurane anesthesia or increasing clinically relevant adverse events.

Many sedative analgesics premedication and routes of delivery to facilitate parental separation have been described in the literature.[20] Oral administration results in low bioavailability because of extensive first-pass metabolism. Intranasal instillation may be preferred over oral administration, as intranasal drug administration is associated with a relatively high bioavailability and is quickly established with minimal discomfort. The bioavailability of intranasal dexmedetomidine using an atomizer has been reported to be 83.8% in children.[21] Furthermore, the mucosal atomization device used in this study delivers an atomized solution to the nasal mucosa that results in rapid absorption of the drug directly into the systemic circulation. Intranasal administration offers the potential of a less invasive and convenient approach to anesthetic premedication in children.

Despite the lack of appropriate pediatric labeling, the intranasal administration of both dexmedetomidine and ketamine have been used successfully for sedation and analgesia in children. Dexmedetomidine has been advocated as an alternative premedication in the field of pediatric anesthesia, given its sedative properties paralleling those of natural sleep with no respiratory compromise. In

this study, the median onset time of sedation with intranasal dexmedetomidine was 24 min, which was comparable to that reported by Sheta et al.[22] However, this slow-onset time after intranasal administration may lead to some inconvenience in the daily routine of a busy clinical setting.

Some authors have proposed combining dexmedetomidine and ketamine for procedural sedation in pediatric patients to overcome the pitfalls of premedication with dexmedetomidine alone.[13,19] The combination of dexmedetomidine with ketamine has a pharmacological rationale, as the two medications exhibit complementary pharmacological effects. For example, bradycardia and hypotension are the most common adverse events associated with dexmedetomidine, and accordingly, patients in the dexmedetomidine group exhibited lower heartbeat values in the preoperative phase, albeit with no intervention required. Thus, ketamine can compensate for the dexmedetomidine-induced cardiovascular depression.

Our results have indicated that a combination of dexmedetomidine and ketamine may effectively accelerate the onset of sedation, and allows children to serenely separate from their parents, and accept mask induction without hemodynamic fluctuation and respiratory compromise. These findings are consistent with those in previous reports.[5,19] Emergence delirium in children is still considered a mysterious complication after sevoflurane anesthesia. However, recent findings have demonstrated that dexmedetomidine premedication is effective in reducing emergence delirium and PONV in children.[4] However, our study was not sufficiently powered to determine statistical differences in PONV.

There are several potential limitations of our study that require clarification. First, the indicated timing of premedication administration is 30 min before general anesthesia according to the pharmacodynamics data and the literature.[5,19] Although, the latest pharmacokinetics study has shown that the median time needed for intranasal dexmedetomidine to achieve peak concentration is 37 min, and the maximal sedative effect is observed 45 min after dosing.[23] This might lead to awaken some dexmedetomidine-sedated patients during mask induction. Second, we did not assess the dose-response relationship of the ketamine-dexmedetomidine combination as a premedication treatment. Data on drug pharmacokinetics for the intranasal route are limited. Thus, the dose of ketamine (2 mg $kg^{-1}$) and dexmedetomidine (2 μg $kg^{-1}$) have been standardized based on our routine clinical practice and previous studies.[8,10] Future studies are warranted to define the optimal dose in the clinical setting. Third, we enrolled patients with restrictive inclusion. This sampling method increased the feasibility of the study completion but it may have potentially limited its generalizability. Lastly, we did not assess the preoperative anxiety scores of the children or those of the parents, which may influence the sedative effects of premedication. Therefore, further studies are warranted to address these limitations.

## Conclusion

In summary, premedication using a combination of intranasal dexmedetomidine and ketamine is associated with improved sedation and higher PSAS and MAS scores than those achieved following premedication with dexmedetomidine alone, with no extension of the emergence time or increase in clinically relevant adverse events.

## Data Sharing Statement

The individual participant data supporting published results, the study protocol, and the statistical analysis plan can be accessed with approval from the principal investigator (Dr. Yanhua Guo, guoyanhua19@126.com) after publication.

## Acknowledgments

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## Disclosure

The authors report no conflicts of interest in this work.

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