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Efficacy of intranasal dexmedetomidine-esketamine sedation for pediatric acceptance of facemask: single-center, double-blind, randomized, controlled trial

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Abstract

Objective We compare the efficacy of intranasal dexmedetomidine (DEX) and DEX-esketamine sedation on pediatric acceptance of face mask.

Methods This single-center double-blind randomized controlled study was conducted at a tertiary hospital affiliated with Shanghai Jiao Tong University. Ninety children aged 1 year to 6 years old and scheduled for elective surgery were randomly allocated in a 1:1 ratio into receiving DEX alone ($n=45$) and DEX-esketamine ($n=45$). DEX and esketamine were used intranasally at doses of 2 μg/kg and 2.0 mg/kg respectively. Children were assessed by an attending anesthesiologist with modified observer's assessment of alertness and sedation (MOAA/S), pediatric separation anxiety scale (PSAS) and mask acceptance scale (MAS). Perioperative adverse events (bradycardia, hypotension, hypoxia, emergence delirium etc.) were recorded.

Results Of 95 patients enrolled, 90 completed the study. The proportion of children who accepted facemask was significantly higher in the DEX-esketamine group compared to the DEX group (86.7% (39/45) vs. 62.2% (28/45), $p=0.008$). Within 30 min after intranasal administration of agents, PSAS scores were similar between the two groups. Children in the DEX group were easily aroused when repositioned from the transferring bed to the operation table. In contrast, those in the DEX-esketamine group maintained a stable level of sedation (MOAA/S scores, median [25th–75th interquartile range], 1 [1, 1] for DEX-esketamine vs. 2 [1, 4] for DEX, $p<0.001$). Furthermore, subgroup analysis found that DEX-esketamine provided better facemask acceptance in children with high anxiety (PSAS ≥ 3). There were

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no significant differences in perioperative heart rate, noninvasive blood pressure and percutaneous arterial oxygen saturation between the two groups. Postoperative extubation time and perioperative adverse events were also comparable between the groups (all $p > 0.05$).

Conclusions For preoperative sedation, combination of DEX with esketamine improved mask acceptance than dexmedetomidine alone, likely due to its superior anxiolytic effect in children with high anxiety.

Trial registration This study was registered in the Chinese Clinical Trial Register (registration no. ChiCTR2400087873, registration date on 6/8/2024).

Keywords Esketamine, Dexmedetomidine, Children, Preoperative sedation, Anxiety

Introduction

Preoperative anxiety is prevalent in children and often intensifies under certain circumstances, such as parental separation and breathing through a facemask [1, 2]. This anxiety can significantly affect children's behavioral, emotional, and physiological responses to surgery [3]. It not only increases heart rate, blood pressure, and oxygen consumption, complicating anesthetic management, but also raises postoperative analgesic requirements and the incidence of emergency delirium [4, 5]. Meanwhile, children experiencing high anxiety or fear often exhibit behavioral resistance, such as screaming, withdrawal, or crying, which creates a challenging and uncomfortable situation for all involved. Therefore, effective strategies to alleviate preoperative anxiety are essential for children, parents and anesthesiologists.

Generally, anxiolytic techniques involve pharmacologic and non-pharmacologic methods for mitigating preoperative anxiety. For non-pharmacologic approaches, the effectiveness of interventions can vary significantly depending on the healthcare team implementing them, as not all care settings have well-established protocols [6, 7]. In contrast, pharmacologic method, such as Dexmedetomidine (DEX), an α_2 receptor agonist, are widely used in pediatric population. Dex has been shown to make parental separation more comfortable and acceptable when administrated preoperatively [8–10]. Notably, dexmedetomidine is characterized by its easy-to-arouse sedation properties [11]. However, in clinical practice, children with high anxiety who awaken from sedative effects of DEX often experience significant difficulty accepting the facemask for oxygenation or inhalational induction.

Esketamine, the dextrorotatory isomer of ketamine, activates N-methyl-d-aspartate receptors and possesses potent anti-anxiety, hypnotic and analgesic properties [12, 13]. When used alone, intranasal administration of esketamine is often an unpleasant experience for children due to adverse side effects, including nausea and a bitter taste [14].However, as an adjuvant to DEX, it remains unclear whether DEX-esketamine can enhance pediatric facemask acceptance, particularly in children with high anxiety.

Therefore, in the present study, we primarily compared the efficacy of DEX-esketamine and DEX on facemask acceptance in children during anesthesia induction. Secondarily, we evaluated the efficacy of DEX-esketamine specifically in children with high anxiety.

Materials and methods

Patients

This prospective study was approved by the institutional review Board of Shanghai Children's Medical Center, Hainan branch (no. SYFYIRB2022005), and was registered with the Chinese Clinical Trial Registry (registration no. ChiCTR2400087873). The procedures followed in this study complied with the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participating children. This article adheres to the consolidated standards of reporting trials (CONSORT) guidelines.

Children aged 1 year to 6 years and scheduled for elective surgery were screened for eligibility at a single tertiary center affiliated with Shanghai Jiao Tong University from August 2024 to September 2024. Patients were excluded if they had one of the following conditions: emergency surgery, arrythmia, preexisting neurologic disease, hepatic or renal dysfunction, fever, or if their parents declined participation.

Randomization and blinding

The children were allocated to either the DEX or DEX-esketamine group using a digital block randomization method, with group allocation and patient number sealed in envelopes. Two nurse anesthetists who were not involved in the study, handled drug preparation and intranasal administration, respectively. An attending anesthesiologist, blinded to group allocation, was responsible for evaluating anxiety and sedation and recording physiological parameters.

For children in both groups, 2 μg kg^{-1} of DEX (Yangtze River Pharmaceutical Co., Ltd., Jiangsu, China) was administered. Ten min later, 2 mg kg^{-1} of esketamine (Hengrui Pharmaceuticals Co., Ltd, Jiangsu, China) were administered for group DEX-esketamine, while the DEX Group receiving an equivalent volume of 0.9% saline.

Both drugs were administrated intranasally in their stock solutions without dilution (DEX at 100 μg ml^{-1} and esketamine at 25 mg ml^{-1}), divided equally between both nostrils, 30 min before anesthesia induction.

Sedation and anesthesia procedures

Upon arrival at the operating center, all children, accompanied by a parent, either sit or lay on a transfer bed. Noninvasive blood pressure (NiBP), heart rate (HR), and pulse oximetry were routinely monitored, with values recorded at 5-min intervals. Sedation agents were administrated according to group allocation. Children were separated from their parents and transferred to the operating theater either the modified observer's assessment of alert and sedation scale (MOAA/S, Supplemental Table S1) score ≤ 2 or after 30 min of observation, even if the MOAA/S score remained > 2.

After entering the operating theater and being repositioned on the operation table, children spontaneously inhaled oxygen via a mask. The mask acceptance score was assessed by the same anesthesiologist. Anesthesia induction agents included 3.0 mg kg^{-1} propofol, 0.3 μg kg^{-1} sufentanil, 0.6 mg kg^{-1} rocuronium, and 0.1 mg kg^{-1} atropine, administrated via peripheral vein catheter established in the ward. Following tracheal intubation, pressure-controlled ventilation with a tidal volume of 8 ml kg^{-1} and an age-adjusted frequency was used to maintain end-tidal carbon dioxide between 35 and 45 mmHg. Sevoflurane and remifentanil were used to maintain anesthesia depth and analgesia, guided by HR and NiBP values [15].

Endpoints

Successful acceptance of the facemask was defined as a mask acceptance scale (MAS, Supplemental Table S2) score ≤ 2. Other endpoints included levels of sedation and anxiety, which were assessed using MOAA/S and pediatric separation anxiety scale (PSAS, Supplemental Table S3). High anxiety was defined as a PSAS score ≥ 3 points lasting for > 2 min. Perioperative adverse events included hypotension, bradycardia, and desaturation. Hypotension was defined as a decrease of > 20% in the mean arterial pressure from baseline and sustained for > 5 min. Bradycardia thresholds were heart rate < 100 beats per minute (bpm) for infants, and < 80 bpm for toddlers and young children. Desaturation was defined as a pulse oxygenation saturation < 95% for > 30 s or < 90%. Emergence delirium was evaluated by the pediatric anesthesia emergence delirium scale (PAED, Supplemental Table S4) and diagnosed with a PAED score ≥ 10 points. Additionally, time to extubation and length of stay in PACU were recorded.

Statistical analysis

Sample size calculation

The primary endpoint of study was the proportion of children who accepted the facemask. Based on our pilot study, the proportions in the DEX group and the DEX-esketamine group were 60% and 80%, respectively. Assuming a two-sided type I error of 0.05 and a power of 80%, the required sample size was estimated to be 86 participants. Accounting for a 10% dropout rate, 95 patients requiring preoperative sedation were planned for enrollment and randomized in a 1:1 ratio.

Data analysis

The normality of continuous data was assessed using the Shapiro-Wilk test. Continuous variables are presented as median and 95% confidence intervals (95% CI), ordinal variables as median and interquartile ranges [IQR; 25th -75th percentiles], and categorical variables as counts and percentages. Non-normally distributed continuous data and ordinal data were compared using the Mann-Whitney U test, while categorical variables were analyzed with the χ^2 test. Continuous variables (e.g., HR and NiBP) between groups were analyzed using repeated measures analysis of variance. All statistical analyses were performed using IBM SPSS Statistics 24 (SPSS, IBM Corporation, Armonk, NY) and GraphPad Prism 8.0 (GraphPad Software Inc, San Diego, CA) software; A p-value < 0.05 was considered statistically significant.

Results

Ninety-five children were recruited, of whom five children did not meet the eligible criteria. Ultimately, 90 children were enrolled in the study, with 45 children assigned to the DEX group and 45 to the DEX-esketamine group. All participants completed the study and were included in the analysis. A detailed flowchart is presented in Fig. 1. There were no significant differences in demographic characteristics between the two groups (all $p > 0.05$, Table 1).

The proportion of children who accepted facemask was significantly higher in the DEX-esketamine group compared to the DEX group (86.7% (39/45) vs. 62.2% (28/45), $p = 0.008$). The MAS score was also lower in the DEX-esketamine group than in the DEX group (median [IQR], 1 [1, 1] vs. 2 [1, 4], $p < 0.001$, Fig. 2. A). These results demonstrate that DEX-esketamine effectively improves mask acceptance.

We also assessed separation anxiety and sedation levels in both groups using the PSAS and MOAA/S scores. Both strategies showed similar effects in ameliorating separation anxiety (Fig. 2B). However, children in the DEX-esketamine group had lower MOAA/S scores at the time of separation from their parents and transfer to the operating theater (median [IQR], 1 [0, 2] vs. 2 [1, 2],

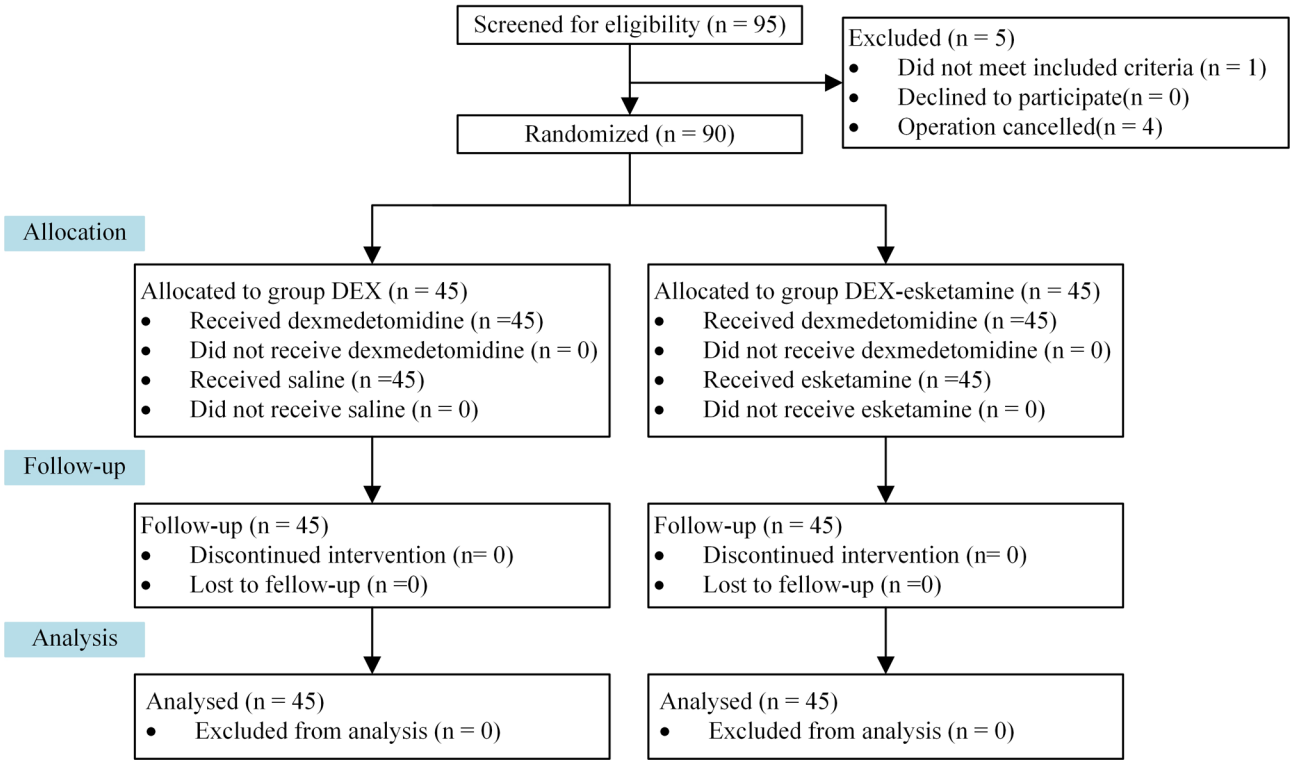

Fig. 1 The flow chart shows numbers of children enrolled, followed up and analyzed in study

$p = 0.003$, Fig. 2C). Notably, when children were repositioned from the transfer bed onto the operating table, the MOAA/S score in the DEX group increased to 4 [IQR 2, 5], which was significantly higher than that in the DEX-esketamine group (vs. 1 [0, 3], $p < 0.001$, Fig. 2C). This finding suggests that children receiving DEX alone are more easily aroused.

Furthermore, we analyzed the relationship between the extent of preoperative anxiety and the sedation effects in the two groups. All children were divided into two subgroups based on their PSAS scores: PSAS ≥ 3 and PSAS < 3. As shown in Fig. 3, for children with high anxiety (PSAS ≥ 3), the DEX-esketamine group had a significantly higher facemask acceptance rate compared to the DEX group (80% (16/20) vs. 27.8% (5/18), $p < 0.001$). However, for children with PSAS < 3, the proportions were comparable between the two groups (92.0% (23/25) vs. 85.2% (23/27), $p = 0.442$). These results suggest that the superior facemask acceptance in the DEX-esketamine group may be related to better relaxation in children with high anxiety.

There were no significant differences in perioperative HR, NiBP and oxygen saturation between the two groups. After sedation, HR and NiBP declined but remained within the acceptable ranges (Fig. 4). Additionally, time to extubation, length of stay in PACU and incidence of postoperative delirium were comparable between the two groups (all $p > 0.05$). Relevant results were shown in Table 2.

Discussion

This study found that children in the DEX-esketamine group had significantly better facemask acceptance during anesthesia induction compared to those in the DEX group. Furthermore, children with high anxiety who received DEX-esketamine demonstrated improved facemask acceptance compared to those who received DEX, whereas children with low anxiety exhibited comparable acceptance in both groups. Additionally, children in the DEX group were more easily aroused, particularly during repositioning from the transferring bed to the operation table, compared to those in the DEX-esketamine group.

Children receiving DEX-esketamine demonstrated better facemask acceptance, with the success rate comparable to the findings of Lu et al. (86.7% vs. 90%) [16]. Esketamine, as an adjunctive agent, enhanced the hypnotic effect of DEX and improved mask acceptance. In addition to preoperative sedation, DEX-esketamine has been used effectively for procedural sedation in pediatric dentistry and MRI [17, 18]. Parental separation and the use of a facemask for preoxygenation or inhalational induction are common but unavoidable situations that can easily provoke anxiety. In this study, both groups exhibited comparable anxiety scores during parental separation, suggesting that both strategies provided effective

Table 1 Patient's demographic and perioperative data

	DEX (*n* = 45)	DEX-esketamine (*n* = 45)	*p* value
Age, y	3.7 (2.9, 3.9)	3.2 (2.9, 3.9)	0.673
Weight, kg	15.0 (13.1, 15.5)	13.8 (12.8, 14.8)	0.399
Height, cm	103 (92, 101)	100 (93,101)	0.673
Gender, n (%)			0.490
Male	30 (66.7)	33 (73.3)	
Female	15 (33.3)	12 (26.7)	
Surgery, n (%)			0.554
General surgery	21 (46.7)	28 (62.2)	
Urological surgery	8 (17.8)	5 (11.1)	
ENT surgery	3 (6.7)	2 (4.4)	
Orthopedic surgery	12 (26.7)	8 (17.8)	
Catheterization	1 (2.2)	2 (4.4)	
ASA-PS, n (%)			0.447
I	3 (6.7)	5 (11.1)	
II	42 (93.3)	39 (86.7)	
III	0	1 (2.2)	
Snoring, n (%)	12 (26.7)	10 (22.2)	0.624
Recent URI, n (%)	9 (20.0)	11 (24.4)	0.612
Allergy, n (%)	13 (28.9)	9 (20.0)	0.327
History of surgery, n (%)	3 (6.7)	4 (8.9)	0.694
Duration of surgery, min	40 (40, 62)	45 (42, 61)	0.399
PSAS, n (%)			0.670
≥ 3	18 (40.0)	20 (42.2)	
≤ 2	27 (60.0)	25 (57.8)	

All data are shown as median (95% CI) or number (%). A p-value < 0.05 was considered statistically significant. Abbreviations: ENT, ear-nose-throat; ASA-PS, American society of anesthesiology physical status; URI, upper respiratory infection

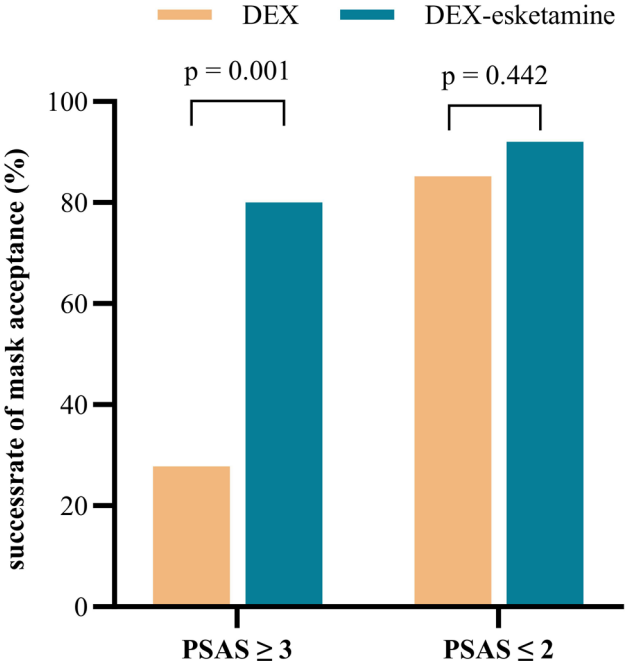

Fig. 3 Subgroup analysis of the success rate of mask acceptance between DEX and DEX-esketamine in children with pediatric separation anxiety scale (PSAS) scores ≥ 3 and <3

sedation. Similar to ketamine, esketamine as adjuvant to DEX resulted in lower MOAA/S scores than either drug used alone [8, 19].

Further, children with high anxiety in group DEX may experience heightened arousal, resulting in lower face-mask acceptance. Anxiety and arousal are correlated, suggesting that addressing one factor could potentially

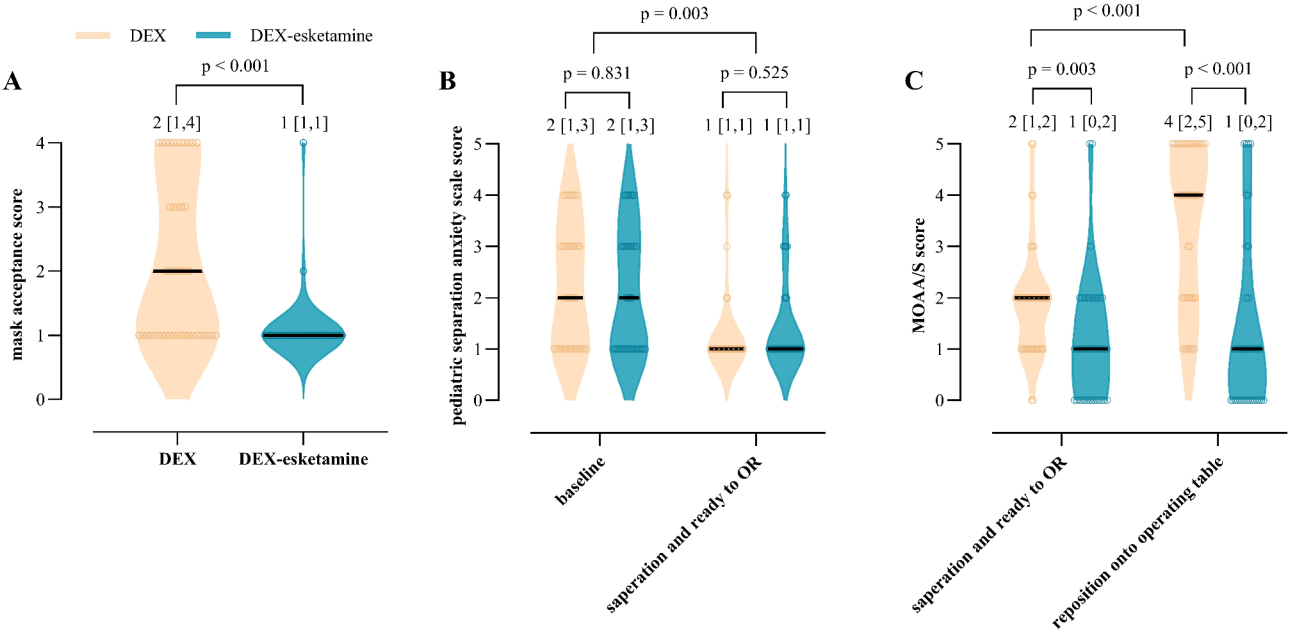

Fig. 2 Mask acceptance scale scores (**A**), pediatric separation anxiety scale scores (**B**) and modified observer's assessment of alertness and sedation (MOAA/S) scores (**C**) in children receiving DEX or DEX-esketamine

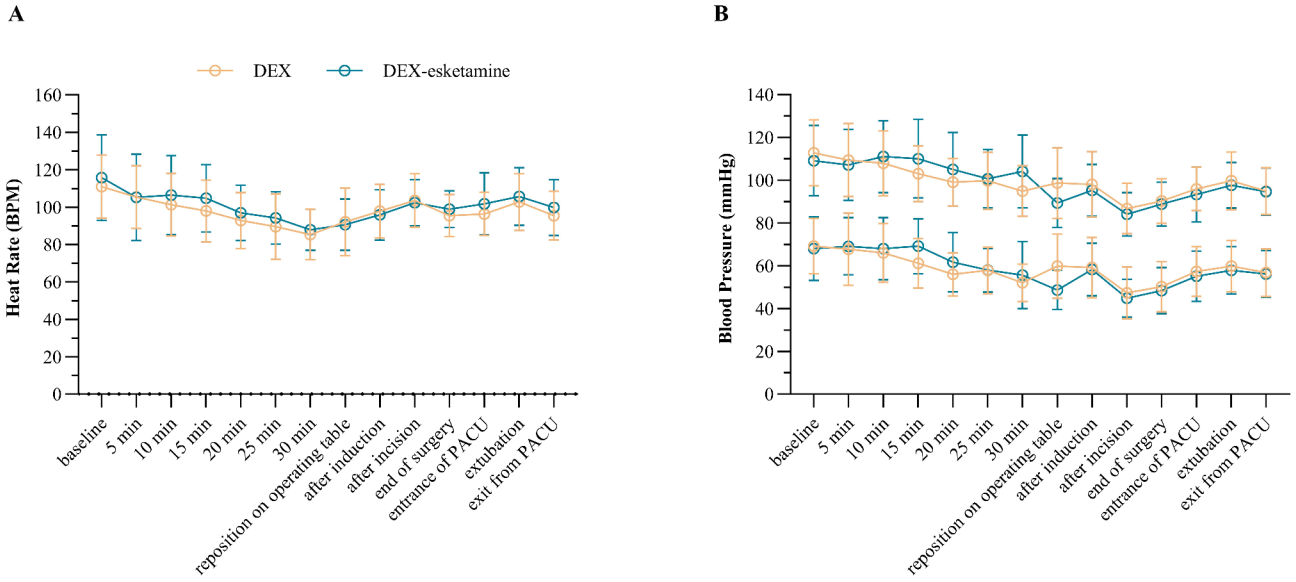

Fig. 4 Changes in heart rate (**A**) and blood pressure (**B**) in children sedated with DEX or DEX-esketamine

Table 2 Duration of anesthesia and perioperative adverse events

	DEX (*n* = 45)	DEX-esketamine (*n* = 45)	*p* value
Time to extubation, min	18 (17, 23)	18 (16, 22)	0.915
LOS in PACU, min	52 (49, 56)	51 (48, 56)	0.898
PAED, n (%)	13 (28.9)	17 (37.8)	0.371

All data are shown as median (95% CI) or number (%). A p-value < 0.05 was considered statistically significant. Abbreviations: LOS, length of stay; PACU, post-anesthesia care unit; PAED, pediatric anesthesia emergence delirium

improve the others [20]. For children exhibiting fear and/or high anxiety, DEX alone may be insufficient to fully disrupt the connectivity between consciousness and the environment, which can be quickly re-established by external stimuli such as body repositioning [21]. This effect may be influenced by the severity of anxiety or stress, as well as the action of dexmedetomidine on α_2 adrenoceptor of norepinephrine neuron in the locus coeruleus and dopamine neurons in the ventral tegmental area [22, 23].

In the present study, DEX and esketamine were administrated at doses similar to those used in the study by Qian et al., and slightly higher than those reported by Lu et al. (1 μg kg^{-1} and 0.5 mg kg^{-1} for DEX and esketamine, respectively) [16, 19]. Different dosages may be tailored to achieve the desired level of sedation. For instance, when preoperative sedation success was defined as a Ramsay Sedation Scale score ≥ 3 and Parental Separation Anxiety Scale score ≤ 2, the ED_{50} of intranasal esketamine was 0.7 mg kg^{-1} [24]. Similarly, for pediatric dental procedures requiring MOAA/S scores of 4, the ED_{95} of intranasal esketamine combined with 0.5 mg kg^{-1} oral midazolam was 1.99 mg kg^{-1} [13].

In this study, considering the higher frequency of extreme anxiety or even phobia observed during the preliminary trials, we selected a combination of 2 mg kg^{-1} esketamine and 2 μg kg^{-1} DEX. Perioperative hemodynamics, including HR and NiBP, remained within acceptable ranges, and no inotropic agents were required. These findings suggest that the selected combination and dosage were well-tolerated and demonstrated an acceptable safety profile.

This study has several limitations that should be acknowledged. First, only one dosage combination of Dex and esketamine was examined in this study. The optimized dosage and the dose-effect relationship of Dex-esketamine can be examined in further research to obtain facemask acceptance without oversedation. Second, factors such as age and preoperative anxiety levels may influence the pharmacological effects of sedative agents [25]. Additional studies are necessary to elucidate the pharmacokinetics and pharmacodynamics of DEX-esketamine in specific pediatric populations. A promising direction for future research would be to compare groups with similar characteristics to assess whether age (e.g., infants vs. preschool children) influences selection effects related to preoperative sedation. Third, most of children in DEX-esketamine group had MOAA/S score ≤ 1 (with or without a response to trapezius squeeze), which may raise concerns about oversedation. The deeper levels of sedation achieved with DEX-esketamine may correlated to the improved facemask acceptance, particularly in highly anxious children. Whether an individualized strategy should be adopted warrants further investigation.

Conclusions

For preoperative sedation, combination of DEX with esketamine improved mask acceptance than dexmedetomidine alone, likely due to its superior anxiolytic effect in children with high anxiety.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-02939-w.

Supplementary Material 1

Supplementary Material 2

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Author contributions
Dr. Zhang K was involved in trial design, performing assessment, formal data analysis, manuscript writing and editing, and funding acquisition. Zhang G participated in preoperative sedation and follow-up. Zhang Y and Wang J contributed to data collection and anesthesia. Dr. Bai supervised patient safety. Dr. Zheng and Dr. Tao were responsible forin conceptualization, methodology validation and overall supervision.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Shanghai Children's Medical Center.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review Board of Shanghai Children's Medical Center Hainan branch (no. SYFYIRB2022005) and was registered with the Chinese Clinical Trial Registry (registration no. ChiCTR2400087873). Prior written informed consent was obtained from all participants. All methods were performed in accordance with the relevant guidelines and regulations of the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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