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CLINICAL TRIAL REPORT

The Impact of Intranasal Esketamine on Emergence Agitation in Children Undergoing Adenotonsillectomy: A Randomized Controlled Study

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Purpose: To investigate the efficacy of intranasal esketamine in reducing the incidence of emergence agitation (EA) in pediatric patients undergoing adenotonsillectomy and to determine the optimal dose of esketamine.

Methods: A total of 204 children aged 3–6 years scheduled for adenotonsillectomy were randomly assigned to three groups. All participants received a standardized anesthetic induction protocol. Following tracheal intubation, they were administered intranasally 0.5 mg/kg esketamine (group LE), 1 mg/kg esketamine (group HE), or an equivalent volume of saline (group C). Anesthesia was maintained with sevoflurane during surgery, and the children were transferred to the post-anesthesia care unit (PACU) after extubation. The highest scores on the Pediatric Anesthesia Emergence Delirium (PAED) scale and the modified Children's Hospital of Eastern Ontario Pain Scale (m-CHEOPS) in the PACU were recorded. The incidence of EA, defined as PAED ≥ 10, was calculated for each group. Additionally, changes in vital signs after intranasal administration, surgery time, anesthesia time, extubation time, eye-opening time, recovery time, and the incidence of adverse reactions were compared among the three groups.

Results: Group LE demonstrated a significantly lower incidence of EA compared with group C (10.45% vs 29.85%, $P = 0.005$), while no significant difference was observed between group LE and HE (10.45% vs 12.12%, $P = 0.760$). Relative to Group C, children in Group LE also showed significantly lower PAED ($P = 0.010$) and m-CHEOPS scores ($P = 0.023$), along with reduced requirements for rescue propofol ($P = 0.005$) and rescue fentanyl ($P = 0.013$). Groups LE and HE demonstrated comparable performance across these secondary outcomes; however, extubation time was prolonged in Group HE ($P = 0.025$).

Conclusion: Intranasal esketamine at a dose of 0.5 mg/kg significantly reduces the incidence of EA following pediatric adenotonsillectomy. Increasing the dose to 1 mg/kg does not confer additional benefit in preventing EA and may instead delay extubation.

Keywords: esketamine, intranasal, adenotonsillectomy, emergence agitation, children

Introduction

Tonsillectomy and adenoidectomy are common pediatric day surgeries. Due to factors such as the young age of the patients, postoperative pain, and inhaled anesthetics, the incidence of emergence agitation (EA) during the recovery period after tonsillectomy and adenoidectomy can be as high as 80%.[1] EA is closely associated with several adverse postoperative events, such as accidental falls, intravenous catheter dislodgement, and surgical wound bleeding, which can delay postoperative recovery and hospital discharge. In addition to optimizing analgesia, pharmacological prophylaxis remains the most used strategy, including agents such as dexmedetomidine,[2,3] midazolam,[3] and gabapentin.[3] Studies have demonstrated that both intranasal and intravenous dexmedetomidine can effectively reduce the incidence of EA,[2] however, the intranasal route provides longer-lasting analgesic and sedative effects while maintaining more stable hemodynamics.

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Esketamine, the dextrorotatory enantiomer of ketamine, exhibits higher affinity for NMDA receptors and μ-opioid receptors compared to its racemic counterpart. It demonstrates approximately twice the potency of ketamine, along with greater systemic clearance and a reduced incidence of adverse effects. Clinical studies have demonstrated that low-dose intravenous esketamine can effectively mitigate emergence agitation (EA) in pediatric patients following tonsillectomy and adenoidectomy.[4] Recent comparative research indicates that intranasal administration of 1 mg/kg esketamine yields a lower incidence of postoperative EA than intranasal dexmedetomidine at a dose of 1 μg/kg.[5] Intranasal administration serves as a non-invasive and convenient approach for drug delivery. Esketamine can be effectively absorbed through the mucosal membrane while bypassing first-pass metabolism, and exert therapeutic effects rapidly owing to the rich vascular plexus of the nasal cavity, which communicates with the subarachnoid space via the olfactory and trigeminal nerves.[6] Compared to intravenous administration, its absorption rate is slower, potentially resulting in a more prolonged therapeutic effect. Clinical studies have demonstrated that intranasal administration of esketamine is an effective therapeutic intervention for depression.[7,8] Furthermore, intranasal esketamine has been shown to mitigate preoperative separation anxiety in pediatric patients and reduce the incidence of EA following strabismus surgery.[9] However, the success of intranasal premedication largely depends on patient compliance, and children aged 3–6 years often have limited cooperation, which may paradoxically heighten perioperative anxiety. To circumvent this issue, intranasal esketamine was administered after tracheal intubation in the present study. Additionally, a low-dose (0.5 mg/kg) was investigated to assess its impact on the incidence of EA following adenotonsillectomy in children aged 3–6 years, and to compare its efficacy with the conventional 1 mg/kg dose.

Materials and Methods

Study Design and Participants

This prospective, double-blind, randomized controlled trial was designed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Approval No.: 2022-K-256-01) and registered with the Chinese Clinical Trial Registry (ChiCTR2300069754). Written informed consent was obtained from the guardians of all participating children. Children between May 2023 to July 2024 scheduled for elective adenotonsillectomy were enrolled. The inclusion criteria were as follows: children aged 3–6 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, with a body mass index (BMI) for age between the 25th and 85th percentiles,[10] and scheduled for elective adenotonsillectomy. Exclusion criteria comprised: recent respiratory infection, excessive nasal secretion, known hypersensitivity to the study medications, psychiatric or neurological disorders, and severe systemic comorbidities.

Intranasal Administration Protocol for Esketamine

In this study, the esketamine hydrochloride injection (Jiangsu Hengrui Pharmaceuticals, Jiangsu, China) was supplied at a concentration of 50 mg/2 mL (25 mg/mL). The group LE received esketamine diluted with normal saline to a concentration of 12.5 mg/mL, whereas the group HE received the undiluted formulation at its original concentration (25 mg/mL). Both groups were administered esketamine at a volume of 0.04 mL/kg. The group C received an equivalent volume of sterile normal saline (0.04 mL/kg), with half of the total dose administered into each nostril.

Procedures

All patients were routinely fasted prior to the procedure: 8 hours for solids, 6 hours for milk/digestible starch, and at least 2 hours for clear fluids, with no preoperative medications administered. Upon arrival in the preoperative preparation room, a 22 or 24 G intravenous catheter was inserted into an upper limb for each child. After being transferred to the operating room, standard anesthesia monitoring was initiated, including electrocardiography, pulse oximetry (SpO_2), and noninvasive blood pressure (NIBP) measurement. Baseline values for heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and SpO_2 were recorded while the children remained calm before anesthesia induction. Lactated Ringer's solution was infused at a rate of 5 $mL\cdot kg^{-1}\cdot h^{-1}$ throughout the procedure. The children were randomly assigned to one of three groups using a random number table: the low-dose esketamine group (0.5 mg/kg, group LE), the high-dose esketamine group (1 mg/kg, group HE), and the control group (group C), with 68 patients in each group. The study medications were prepared by an unblinded researcher. Anesthesia induction was achieved by sequential intravenous administration of atropine (0.01 mg/kg), propofol (3 mg/kg), fentanyl (2 μg/kg), and cisatracurium (0.05 mg/kg), along with inhalation of 3% sevoflurane (100% oxygen at 5 L/min). Two minutes later, tracheal intubation was performed by an experienced anesthesiologist using a video laryngoscope, followed by connection to the anesthesia machine for mechanical ventilation. The ventilation parameters were set as follows: fraction of inspired oxygen of 0.5, an inspiratory-to-expiratory ratio of 1:1.5, and adjusted tidal volume and respiratory rate to maintain end-tidal carbon dioxide pressure between 35–45 mmHg. The fresh gas flow was maintained at 2 L/min, and anesthesia was maintained with 2–4% sevoflurane. The medication preparation personnel prepared the drugs according to the randomized allocation protocol, after which another researcher administered them intranasally to the children. Both the researcher responsible for drug administration and the outcome evaluator were blinded to group assignments. The MAP, HR, and SpO_2 were recorded for children in all three groups at the following time points: before anesthesia induction (T0), at 1 min (T1), 3 min (T2), 5 min (T3), and 10 min (T4) after intranasal esketamine administration. At the end of the surgery, sevoflurane was discontinued. After suctioning oral secretions, no further physical stimulation was applied. The tracheal tube was removed upon resumption of spontaneous breathing with a tidal volume greater than 5 mL/kg, a respiratory rate above 10 bpm, and absence of significant bleeding or airway compromise. In the post-anesthesia care unit (PACU), each child was assessed every 5 minutes using the Pediatric Anesthesia Emergence Delirium (PAED) scale and the modified Children's Hospital of Eastern Ontario Pain Scale (m-CHEOPS), with the maximum scores recorded for analysis. Additionally, the eye-opening time (defined as the duration from extubation to first eye opening) and the incidence of adverse events, including laryngospasm, respiratory depression (SpO_2 < 90% with oxygen supplementation via face mask), and postoperative nausea or vomiting (PONV) were documented. Children were discharged from the PACU upon achieving an Aldrete recovery score of ≥ 9.

Ketorolac tromethamine (0.5 mg/kg) was administered 10 minutes after tracheal intubation for postoperative analgesia, followed by ondansetron (0.1 mg/kg) for PONV prophylaxis. Supplemental fentanyl boluses (0.5–1 μg/kg) were administered when hemodynamic parameters (blood pressure or HR) exceeded 20% above baseline values despite adjustment of sevoflurane concentration.

EA is defined by a PEAD ≥ 10. Severe agitation, indicated by a PEAD ≥ 15, may be treated with intravenous propofol (1–2 mg/kg). If the m-CHEOPS ≥ 6, fentanyl (0.5 μg/kg) should be administered.

Observed Parameters

The Primary Outcome

The incidence of EA is assessed.

The Secondary Outcome

The following parameters were assessed following intranasal esketamine administration: MAP, HR, SpO_2, surgery time (defined as the duration from surgery start to surgery end), anesthesia time (measured from anesthesia start to discontinuation of sevoflurane), extubation time (interval between surgery completion and tracheal extubation), eye-opening time, recovery time (duration from PACU admission to discharge), the maximal PAED score and m-CHEOPS score, the incidence of rescue propofol for EA, incidence of rescue fentanyl, and incidence of adverse events.

Statistical Analysis

According to the the study by Aono et al, the incidence of EA in children under sevoflurane anesthesia is approximately 40%.[11] In our pilot study, the incidence of EA decreased to around 16% following intranasal administration of low-dose esketamine. Assuming that the α error is 0.025 (0.05/2, group LE vs C and group LE vs HE) and the power is 0.80, the sample size required for each group was 62 cases using PASS software. Considering a 10% dropout rate, 68 cases per group were planned for inclusion. Statistical analyses were conducted using SPSS software (version 25.0; SPSS Inc., IBM, Chicago, IL, USA). Normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median (interquartile range). Comparisons between groups were performed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, with Dunn's post hoc test for pairwise comparisons (group LE vs C and group LE vs HE). Median differences (and 95% CI) were calculated with Hodges–Lehmann estimators. Categorical variables were summarized as numbers (percentages) and compared using chi-square test or Fisher's exact test, as appropriate, followed by Bonferroni post hoc correction. Odds ratios (ORs) with 95% CIs were reported. For repeated-measures data, a repeated-measures ANOVA was applied. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Figure 1. Of the 251 subjects screened, 204 eligible children were finally randomized into the three groups. One child in group LE and one child in group HE underwent a change in the surgical plan, while one child in group HE and one child in group C experienced postoperative bleeding. Ultimately, 67 children in group LE, 66 children in group HE and 67 children in group C were included in the final analysis (Figure 1). The baseline characteristics, including age, sex, and BMI, as well as the surgery and anesthesia times of the three groups were similar (Table 1).

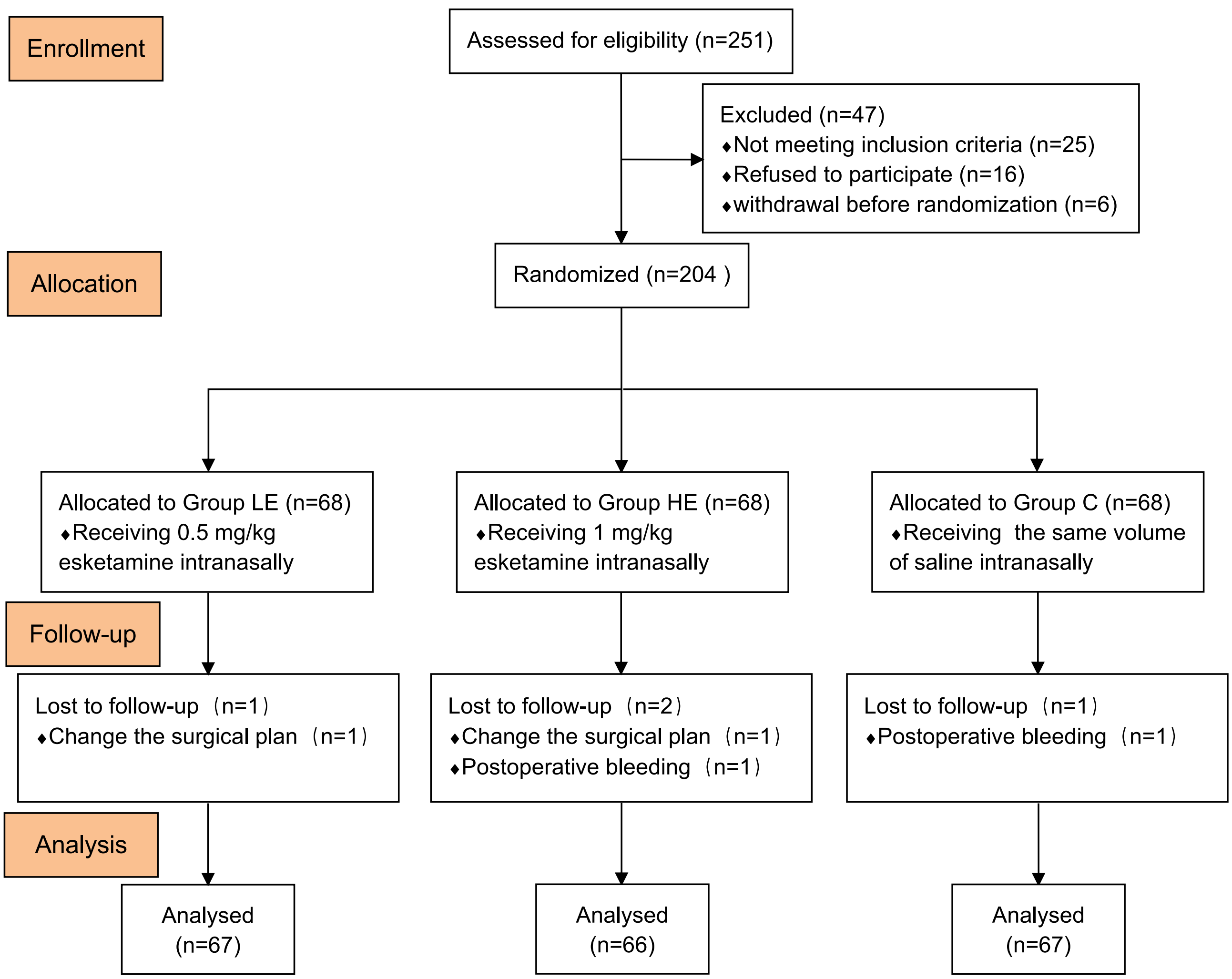

Figure 1 CONSORT flow diagram for study participation.

Table 1 Demographic and Peri-Operative Characteristics

	Group LE (n=67)	Group HE (n=66)	Group C (n=67)	H/χ^2	P value
Age, yr	4 (4–5)	5 (4–6)	5 (4–6)	2.999	0.223
Sex, Male/Female	49/18	38/28	43/24	3.568	0.168
BMI, kg/m^2	15.68 (14.97–16.60)	15.40 (14.96–16.34)	15.40 (14.83–16.60)	0.873	0.646
Surgery time, min	19.00 (18.00–21.00)	18.00 (17.00–22.25)	18.00 (16.00–23.00)	4.330	0.115
Anesthesia time, min	33.00 (32.00–36.09)	33.00 (32.00–38.25)	32.00 (30.00–39.00)	1.794	0.408

Note: Data are presented as median (interquartile range) or number.
Abbreviations: BMI, body mass index; Group LE, low-dose esketamine group; Group HE, high-dose esketamine group; Group C, control group.

Changes in MAP and HR After Intranasal Esketamine Administration

The MAP and HR of the three groups at different time points were analyzed using repeated-measures ANOVA. The results demonstrated a significant main effect of time on both MAP and HR across the three groups (all $P < 0.001$), indicating that their MAP and HR showed significant temporal trends. Pairwise comparisons of MAP and HR at each time point among the three groups revealed no statistically significant differences (all $P > 0.05$). Analysis of the main group effect similarly showed no significant differences in MAP and HR across groups (all $P > 0.05$), indicating that group assignment did not significantly affect children's MAP or HR measurements. Furthermore, the group-by-time interaction effect was not statistically significant (all $P > 0.05$), demonstrating that MAP and HR followed similar temporal patterns across all three groups (Figure 2).

Comparison of Recovery Quality Following General Anesthesia

Compared with group C, group LE showed significant reductions in both maximal PAED (median difference, −2.00; 95% CI: −3.00 to 0.00; $P = 0.010$) and m-CHEOPS scores (median difference, −1.00; 95% CI: −2.00 to 0.00; $P = 0.023$). No statistically significant differences in these two scores were observed between groups LE and HE. However, the extubation time was significantly longer in group HE than in group LE (median difference, −1.00 min; 95% CI: −2.00 to 0.00 min; $P = 0.025$). Statistically significant differences were not detected in eye-opening time or recovery time across the three groups (all $P > 0.05$) (Table 2).

Comparison of Adverse Reactions

The results of adverse reactions were reported in Table 3. EA was observed in 7 of 67 (10.45%) children in group LE, 8 of 66 (12.12%) children in group HE (group LE vs HE; OR, 0.85; 95% CI: 0.29 to 2.48; $P = 0.760$), and 20 of 67

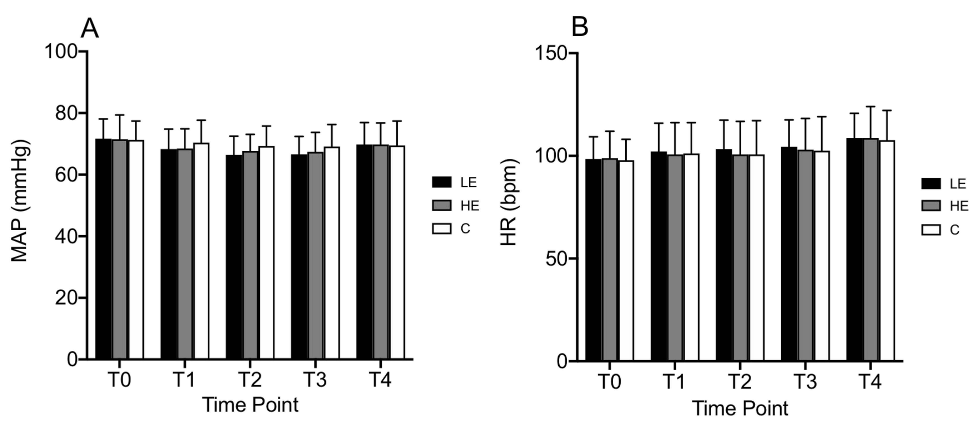

Figure 2 Hemodynamic changes of children among the three groups. (**A**) MAP; (**B**) HR.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; Group LE, low-dose esketamine group; Group HE, high-dose esketamine group; Group C, control group.

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Table 2 Comparison of Recovery Quality After General Anesthesia

	Group LE (n=67)	Group HE (n=66)	Group C (n=67)	*H*	*P*
Extubation time (min)	3.00 (2.00–5.00)	4.00 (2.00–8.00)*	3.00 (2.00–5.00)	8.386	0.015
Eye-opening time (min)	20.00 (14.00–27.00)	23.00 (15.00–32.25)	19.00 (14.00–26.00)	3.860	0.145
Recovery time (min)	30.00 (23.00–36.00)	30.00 (24.00–41.25)	28.00 (22.00–34.00)	3.969	0.137
Maximal PAED score	6.00 (4.00–8.00)	6.00 (3.00–8.00)	8.00 (5.00–11.00)*	9.547	0.008
Maximal m-CHEOPS score	2.00 (2.00–4.00)	2.00 (2.00–4.25)	3.00 (2.00–7.00)*	8.618	0.013

Notes: *$P<0.05$ versus Group LE. Data are presented as median (interquartile range).
Abbreviations: Group LE, low-dose esketamine group; Group HE, high-dose esketamine group; Group C, control group; CI, confidence interval; N/A, not applicable; PAED, Pediatric Anesthesia Emergence Delirium; m-CHEOPS, modified Children's Hospital of Eastern Ontario Pain Scale.

Table 3 Comparison of Postoperative Adverse Reactions

	Group LE (n=67)	Group HE (n=66)	Group C (n=67)	χ^2	*P*
EA	7 (10.45)	8 (12.12)	20 (29.85)*	10.710	0.005
Incidence of rescue propofol	2 (2.99)	3 (4.55)	12 (17.91)*	11.576	0.003
Incidence of rescue fentanyl	9 (13.43)	8 (12.12)	21 (31.34)*	10.011	0.007
Laryngospasm	0	1 (1.51)	1 (1.49)	1.262	0.774
Respiratory depression	0	0	0	–	N/A
PONV	0	1 (1.51)	0	1.848	0.330

Notes: *$P<0.05$ versus Group LE. Data are presented as number (%).
Abbreviations: Group LE, low-dose esketamine group; Group HE, high-dose esketamine group; Group C, control group; CI, confidence interval; EA, emergence agitation; N/A, not applicable; PONV, postoperative nausea or vomiting.

(29.85%) children in group C (group LE vs C; OR, 0.27; 95% CI: 0.11 to 0.70; $P = 0.005$). Two of 67 (2.99%) children in group LE, 3 of 66 (4.55%) children in group HE (group LE vs HE; OR, 0.65; 95% CI: 0.10 to 4.00; $P = 0.636$), and 12 of 67 (17.91%) children in group C (group LE vs C; OR, 0.14; 95% CI: 0.03 to 0.66; $P = 0.005$) needed rescue propofol. Nine of 67 (13.43%) children in group LE, 8 of 66 (12.12%) children in group HE (group LE vs HE; OR, 1.13; 95% CI: 0.41 to 3.12; $P = 0.821$), and 21 of 67 (31.34%) children in group C (group LE vs C; OR, 0.34; 95% CI: 0.14 to 0.81; $P = 0.013$) needed rescue fentanyl.

In group HE, one case of laryngospasm and one case of PONV were observed, whereas one case of laryngospasm occurred in group C. However, there were no significant differences in the incidence of adverse reactions such as laryngospasm, respiratory depression, and PONV among the three groups ($P > 0.05$).

Discussion

This study assessed the efficacy and safety of intranasal esketamine in reducing the incidence of EA in children aged 3–6 years undergoing adenotonsillectomy under sevoflurane anesthesia. Results of the present study demonstrated that a low-dose of 0.5 mg/kg intranasal esketamine significantly reduced incidence of EA and provided better postoperative analgesia than the placebo. These efficacies were comparable to those achieved with the 1 mg/kg high-dose regimen. However, high-dose regimen showed a prolonged extubation time. Furthermore, neither dose of esketamine was associated with an increased incidence of other adverse events, indicating a favorable safety profile.

Tonsillectomy and adenoidectomy in children involve surgical procedures in the pharynx, and inadequate anesthesia management can lead to significant hemodynamic fluctuations. Postoperative pain and pharyngeal discomfort may also increase the risk of EA. Various adjuvant anesthetic agents have been employed to effectively reduce postoperative EA, including sedatives and analgesics such as sufentanil, midazolam, propofol, ketamine, and dexmedetomidine.[12] However, these agents may be associated with adverse effects such as delayed emergence, respiratory depression, nausea, and vomiting. Therefore, identifying optimal drugs and dosages remains crucial.

Esketamine possesses sedative and analgesic properties. It requires only half the dose of racemic ketamine to achieve satisfactory anesthetic effects while inducing fewer psychiatric side effects.[13] Previous studies have demonstrated that intravenous ketamine can reduce EA in children following sevoflurane anesthesia.[14–16] Furthermore, research indicates that intravenous esketamine is also effective in mitigating postoperative EA.[4,17] Intranasal administration offers a slower onset, a prolonged duration of action, and fewer adverse effects compared to intravenous injection. Evidence suggests that intranasal esketamine is clinically useful in treating depression,[18,19] supporting the theoretical feasibility of its use in pediatric surgical settings. This study found that intranasal administration of 0.5 mg/kg esketamine significantly reduced the incidence of EA in pediatric patients, with an effect comparable to that of the 1 mg/kg dose, consistent with recent findings from another study.[2] Postoperative pain is widely regarded as a major contributor to EA.[20] Esketamine has been shown to provide effective postoperative analgesia[21,22] and improve pain outcomes in children undergoing tonsillectomy when administered via nasal drops.[23] The present study also demonstrated that the m-CHEOPS scores and the need for rescue fentanyl were lower in the esketamine groups compared to the control group. These findings suggest that the analgesic properties of esketamine may contribute to its efficacy in reducing EA incidence.

The clearance rate of esketamine is higher than that of ketamine, resulting in a lower incidence of adverse reactions. In this study, no significant differences were observed in hemodynamic trends within the first 1–10 minutes following intranasal administration across the three groups, suggesting that intranasal esketamine does not markedly affect hemodynamic stability in pediatric patients. Additionally, Li et al reported that intravenous administration of 0.25 mg/kg esketamine at the end of surgery delayed eye-opening time.[4] However, in this study, the eye-opening time of children in the esketamine groups was not delayed. This may be attributed to the earlier administration of esketamine and its relatively milder absorption via the nasal mucosa, leading to pharmacokinetic differences compared to intravenous injection. In this study, the group HE exhibited prolonged extubation time, which could be due to the synergistic effect of the higher esketamine dose with anesthetic agents, thereby delaying the recovery of spontaneous respiration in children. Additionally, the incidence of adverse reactions—such as laryngospasm, respiratory depression, and postoperative nausea and vomiting (PONV)—was low across all three groups. These findings may suggest the high safety profile of intranasal administration of 0.5 mg/kg esketamine in preschool children undergoing adenotonsillectomy. In children experiencing EA in the PACU, intranasal esketamine may be considered as a potential intervention, though further research is warranted to establish its efficacy and safety.

This study has several limitations. First, preoperative anxiety in children was not assessed, which may influence the effectiveness of EA. Second, there was no follow-up evaluation of postoperative behavioral changes or analgesic outcomes. Third, no comparisons were made with other sedative-analgesic drugs. Additionally, pharmacokinetic analysis of intranasal esketamine was not conducted. Furthermore, this was a single-center study, and thus, the findings require validation through more high-quality, multicenter investigations.

Conclusion

Intranasal esketamine at a dose of 0.5 mg/kg significantly reduces the incidence of EA following pediatric adenotonsillectomy. Increasing the dose to 1 mg/kg does not confer additional benefit in preventing EA and may instead delay extubation.

Abbreviations

ASA, American Society of Anesthesiologists; ANOVA, Analysis of variance; BMI, Body mass index; CI, Confidence interval; C, Control group; CONSORT, Consolidated Standards of Reporting Trials; DBP, Diastolic blood pressure; EA, Emergence agitation; HE, High-dose esketamine group; HR, Heart rate; LE, Low-dose esketamine group; MAP, Mean arterial pressure; m-CHEOPS, modified Children's Hospital of Eastern Ontario Pain Scale; NIBP, Noninvasive blood pressure; OR, Odds ratios; PACU, Post-anesthesia care unit; PAED, Pediatric anesthesia emergence delirium; PONV, Postoperative Nausea or Vomiting; SBP, Systolic Blood Pressure; SpO_2, pulse oximetry.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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