



Compare the Effects of 0 mg/kg, 0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg Esketamine on Emergence Agitation After Tonsillectomy and Adenoidectomy in Children: A Randomized Control Trial

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Background: The probability of children experiencing emergence agitation (EA) in post-anesthesia care unit (PACU) undergoing adenoidectomy and tonsillectomy is up to 80%. This study investigated the effects of pre-anesthesia sedation of esketamine at 0mg/kg (Control group), 0.1mg/kg, 0.3mg/kg and 0.5mg/kg on EA in children.

Methods: 164 children aged 3–10 years, with American Society of Anesthesiologists (ASA) class I–II were included. Children were randomly divided into groups k_0 , k_1 , k_3 and k_5 , and the intravenous anesthesia doses of esketamine were 0 mg/kg, 0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg, respectively. EA occurrence was assessed using the Pediatric Anesthesia Emergence Delirium Scale (PAED) and Watcha scale. Anesthesia time, operation time, tracheal catheter removal time, PACU stay time, hospital stay, postoperative face, legs, activity, crying, consolability scale (FLACC), analgesia needs, heart rate (HR), mean arterial pressure (MAP) at different times, and postoperative complications were also recorded in the four groups.

Results: There were significant statistical differences in PAED scores [13.00 (7.75), 10.00 (6.00), 9.00 (4.00), 9.00 (2.00), $p=0.002$], Watcha scores [3.00 (1.00), 3.00 (1.00), 2.00 (1.00), 2.00 (1.00), $p<0.001$], occurrence of postoperative EA [25 (62.5%), 21 (56.8.8%), 10 (25.6%), 7 (18.9%), $p<0.001$], and severe postoperative EA [20 (50.0%), 11 (29.7%), 4 (10.3%), 3 (8.1%), $p<0.001$] among the groups k_0 , k_1 , k_3 and k_5 . There were no significant differences in operation time, duration of anesthesia, postoperative analgesia and antiemetic needs, and residence time in the PACU among the 4 groups ($p>0.05$). The 0.5 mg/kg group significantly increased the time required for tracheal catheter removal ($p<0.05$). The differences in HR and MAP among the four groups were statistically significant ($p<0.05$).

Conclusion: Intravenous administration of esketamine at dose of 0mg/kg, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg before anesthesia induction leads to differences in the PAED score and incidence of EA of children after adenoidectomy and tonsillectomy. 0.3 mg/kg esketamine appears to offer the optimal balance between efficacy and safety in reducing EA.

Trial Registration Number: ChiCTR2300075038. The trial is publicly available and is registered at www.chictr.org.cn on August 23, 2023.

Keywords: adenoidectomy, tonsillectomy, children, emergence agitation, EA, esketamine

Introduction

Adenoidectomy and tonsillectomy are among the common surgical operations in pediatric patients.¹ However, the incidence of emergence agitation (EA) in the post-anesthesia care unit (PACU) following these procedures can be as

high as 80%.^{2,3} Although EA in children is typically self-limiting, it has potential medical risks, such as turning over and falling off the bed, venous tube slipping, and postoperative wound bleeding, which can endanger the safety of children in serious cases.⁴ Additionally, EA increases the workload of nursing staff, and often needs to physically restrain children and reduce parental satisfaction with the anesthesia process.⁴ Various medications, including midazolam, propofol, opioids and dexmedetomidine have been shown to reduce the incidence and severity of EA in children after surgery,^{5–8} among which dexmedetomidine is more commonly used. However, these drugs are associated with adverse effects such as injection pain, hemodynamic instability, postoperative respiratory depression, increased the time to eye-open and the time to PACU discharge, which are not conducive to postoperative rehabilitation of children.^{9–11} Although early sedation and analgesia can reduce the occurrence of postoperative agitation, there are still patients receiving general anesthesia who are given sufficient sedation and analgesia to develop postoperative agitation.¹² Thus, managing postoperative EA remains a significant challenge for anesthesiologists. Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist, is an effective sedative, analgesic, and amnesia drug, and its effect on reducing the incidence of EA has been demonstrated by many studies.^{13,14} Esketamine, the S-enantiomer of ketamine, is a high-affinity antagonist of the NMDA receptor (with an affinity twice that of ketamine). By blocking the NMDA receptor, it inhibits glutamergic signal transmission, reduces central sensitization and hyperalgesia, and has a more reliable sedative and analgesic effect than racemic ketamine. And it has a relatively low risk of mental and cognitive adverse reactions.¹⁵ Esketamine can inhibit the release of pro-inflammatory factors such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and interleukin-6 (IL-6), reduce the stimulation of postoperative inflammatory responses in the central nervous system, and promote the recovery of postoperative cognitive function.¹⁶ Therefore, esketamine is a typical intravenous anesthetic commonly used before surgery and has unique advantages in diagnostic testing and short operating time in children. Liu's et al, research based on esketamine anesthesia (1 mg/kg) found that it could relieve postoperative pain and regulate inflammatory responses in children undergoing endoscopic plasma tonsillectomy.¹ Li et al found that the use of 0.25mg/kg esketamine before the end of the surgery could reduce the incidence of emergency agitation in children undergoing tonsillectomy, without prolonging the extubation time or increasing postoperative side effects.¹⁷ However, the results of a cohort study showed that the induction of near-anesthetic single dose esketamine (the average dose was 0.46 mg/kg) may increase the incidence of EA after minor surgery in preschool children, and the incidence of EA in high-dose esketamine (>0.3, \leq 0.5; >0.5 mg/kg) is higher than that in low-dose group (0; >0, \leq 0.3 mg/kg).¹⁸ Therefore, the dosage of esketamine is particularly important in clinical practice to reduce the incidence of EA in pediatric patients. The main purpose of this study is to explore the effects of esketamine at doses of 0 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg before anesthesia on EA after adenoidectomy and tonsillectomy in children. We hypothesize that esketamine at doses of 0 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg can reduce the occurrence of postoperative EA to varying degrees, which is helpful for anesthesiologists to provide clinical guidance for reducing EA during the postoperative anesthesia recovery period.

Methods

This prospective, equally randomized (1:1), double-blind, parallel-group trial was conducted at the Affiliated Hospital of the North Sichuan Medical College. Ethical approval was obtained from the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (approval number: 2023ER270-1; July 18, 2023). This study was registered at the Chinese Clinical Trial Center (www.chictr.org.cn), registration number ChiCTR2300075038, registration date August 23, 2023. Written informed consent was obtained from the parents or legal guardians of all participants. The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the protocols were conducted in accordance with the tenets of the Declaration of Helsinki.

This clinical trial was conducted between September 2023 and November 2024. We enrolled 164 patients who underwent plasma tonsil adenoidectomy. The inclusion criteria were 3–10 years old, body mass index (BMI) 18–28 kg/m²; American Society of Anesthesiologists (ASA) physical status of I–II with documented normal cardiopulmonary, hepatic, and renal function; operation expected to last 20–60 minutes; The exclusion criteria were as follows: body weight less than 10 kg; children undergoing emergency surgery; a history of allergy to opioid or non-opioid analgesics; a history of respiratory infection or asthma; developmental delays or psychiatric disorders associated with symptoms

such as irritability, anxiety, attention deficit, sleep disturbance, or cognitive impairment; children with difficult airways for preoperative assessment; and inability to complete the trial for other reasons.

According to the random number table method, all patients were divided into groups k_0 , k_1 , k_3 and k_5 with 41 patients in each group. The doses of intravenous injection of esketamine (Jiangsu Hengrui Pharmaceutical Co., LTD., China) in groups k_1 , k_3 and k_5 were 0.1mg/kg, 0.3 mg/kg and 0.5 mg/kg respectively. In group k_0 , the same volume of normal saline was intravenously injected. Nurses randomly distributed the corresponding concentrations of esketamine to 10mL syringes, sealed the envelopes and kept them for later use. None of the patients and their families, investigators, anesthesiologists, surgeons, or data collectors were unaware of patient assignment.

All children fasted for 8 h and were forbidden to drink for 4 h before surgery, and no preoperative drugs were used. The venous passage of one forearm was opened with a size 24 indwelling venous needle, accompanied by parents or other family members in the pre-operative holding area. Electrocardiography (ECG), blood oxygen saturation (SpO_2), noninvasive systolic blood pressure (SBP), noninvasive diastolic blood pressure (DBP), and heart rate (HR) were routinely monitored after admission to the operating room. The anesthesiologist opened the envelope handed by the nurse and provided an intravenous infusion of the premade esketamine solution. The Ramsay sedation scale(RSS)¹⁹ was used to evaluate sedation depth and the RSS criteria were defined as follows: 1=awake; 2=awake, cooperative, orientated, and tranquil; 3=awake, responds to commands only; 4=asleep, reacts with a brisk response to a light glabellar tap or a loud auditory stimulus; 5=asleep, reacts with a sluggish response to a light glabellar tap or a loud auditory stimulus; 6=asleep, does not respond to pain. Anesthetic induction drugs included propofol 2 mg/kg, fentanyl 3 μ g/kg, rocuronium 0.6 mg/kg for tracheal intubation. All children were intubated successfully by anesthesiologists with more than three years of anesthesia experience. During the operation, sevoflurane with 3% concentration was inhaled and remifentanyl was administered intravenously at a rate of 0.06–0.2 μ g/kg/min to maintain the depth of anesthesia, and the heart rate (HR) and mean arterial blood pressure (MAP) of the children were maintained to not exceed or lower than 30% of the preoperative level. All the children underwent tonsillectomy and adenoidectomy performed by the same group of surgeons. The anesthesiologist turned off the inhalation anesthesia, discontinued the intravenous injection of remifentanyl at the end of the procedure, and provided 100% oxygen at 6 L/min. Neostigmine (0.04 mg/kg), and atropine (0.015 mg/kg) were used to reverse the residual neuromuscular block after surgery, and excess secretions were completely removed from the child's mouth. When the child had significant spontaneous breathing and purposeful movement, the tracheal catheter was removed and the child was transferred to the PACU. Children whose operation time exceeds one hour or is less than 20 minutes will be excluded from the trial.

The occurrence of EA after anesthesia in children was evaluated every 10 minutes starting from when the children entered the PACU using the Pediatric Anesthesia Emergence Delirium (PAED)²⁰ and Watcha scales,²¹ and the highest scores of the PAED and Watcha scales were recorded. The PAED scale assesses five items (eye contact, purposefulness of actions, awareness of surroundings, restlessness, and inconsolability) on a scale of 0 to 4, yielding total scores from 0 to 20. The Watcha scale was defined as follows: 1 = cooperative quiet; 2 = mildly upset, crying but soothing; 3 = crying but not soothing; 4 = fidgety, moving hands and feet, and completely uncontrollable. A PAED score greater than or equal to 12 or a Watcha score greater than or equal to 3 was defined as EA during recovery. PAED scores greater than or equal to 14 or Watcha scores greater than or equal to 4 were defined as severe EA during recovery. If severe EA occurs, propofol 1 mg/kg is given intravenously.

Postoperative pain was assessed using the Face, Legs, Activity, Cry, Consolability scale (FLACC),²² FLACC scale was classified as follows: 0 = no pain; 1–3 = slight pain, can tolerate; 4–6 = patients with pain and affect sleep, can still tolerate; 7–10 = the patient has a growing pain, the pain is unbearable. When the postoperative FLACC scores were ≥ 7 , patients were administered intravenous fentanyl 1 μ g/kg. The incidence of postoperative nausea and vomiting (PONV) was assessed using a standardized 4-point scale (0=none, 1=nausea only, 2=single vomiting episode, 3=recurrent vomiting) at 15-minute intervals during PACU stay. If there was severe PONV (PONV score ≥ 2 occurred or persistent retching was observed), ondansetron was given 0.1 mg/kg. If the child had respiratory depression in the PACU (SPO_2 <95%, respiratory rate <12 times/min), the mask-assisted oxygen supply was 5–6 L/min, and the patient was transferred to the ward when the modified Aldrete post-anesthesia score^{23,24} was > 9 points. Ibuprofen was routinely administered at 10 mg/kg/day after the patient was transferred to the hospital.

The primary outcome of this study was the highest PAED score among the children in the PACU. Secondary outcome measures were as follows: 1. The highest Watcha score, probability of postoperative EA, and severe postoperative EA in children during PACU; 2. Ramsay scores of children after entering the operating room and after esketamine administration; 3. The HR and MAP of the children were recorded after entering the operating room (T_1), 3 min after administration of esketamine (T_2), after tracheal intubation (T_3), after tracheal catheter removal (T_4), when entering the PACU (T_5), 5 min after entering the PACU (T_6), 10 min after entering the PACU (T_7), and 15 min after entering the PACU (T_8), time of leaving the PACU (T_9), 4. Postoperative FLACC score and demand for analgesic drugs and intraoperative use of remifentanyl; 5. Tracheal catheter removal time (the time from the end of the operation to tracheal extubation), duration of the operation (the time from the beginning to the end of the surgery), duration of anesthesia (the time from the intravenous injection of esketamine to the cessation of anesthesia), time of residence in the PACU (the time from entering the PACU to leaving the PACU), length of hospital stay (the time from postoperative transfer to ward to discharge), 6. Incidence of PONV, utilization rate of antiemetic drugs, respiratory depression, oxygen desaturation, somnolence, and hallucinations after tracheal extubation.

Based on preliminary data (four-group ANOVA; means = 11, 10, 9, 8; $\sigma = 1.79$; $\eta^2 = 0.28$), we computed the required sample size using PASS 2021. Assuming $\alpha = 0.05$ (two-tailed), 80% power, and a 10% attrition rate, 41 participants per group ($n=164$) were needed.

Statistical analyses were performed using SPSS 21.0 software. The Shapiro–Wilk test was used to assess data normality. Continuous distributed variables were reported as mean \pm standard deviation ($M \pm SD$) or median (interquartile range) [$M(IQR)$], and categorical data were presented as a number (frequency) when appropriate. Quantitative variables between the study groups were compared using one-way ANOVA or the non-parametric Kruskal–Wallis H -test, and pairwise comparisons between groups were conducted using the Bonferroni method. The general linear repeated-measures analysis of variance was used to compare individual indices at multiple time points among the four groups. To compare categorical data, the chi-squared (χ^2) test was performed, and Fisher's exact test was used when appropriate. $p < 0.05$ was considered statistically significant.

Results

In total, 164 children were included in this study between September 2023 and October 2024. Patients were excluded intraoperatively if surgical duration deviated from the predefined 20–60 minutes window and discontinued intervention. The excluded cases (1, 4, 1, and 4 in k_0 , k_1 , k_3 and k_5 groups, respectively) represent protocol-defined exclusions, not post-randomization dropouts due to patient preference or loss to follow-up. These patients were enrolled and received the assigned study drug but were excluded from efficacy analyses because their surgical duration deviated from the predefined 20–60 minutes window, which was essential to control confounding from variable drug exposure times. In the group k_3 , 1 patient underwent a second operation because of postoperative bleeding and was dropout from the analysis. In total, 153 children were included in the analysis (Figure 1). There were no significant differences in the demographic characteristics of the four groups of children ($p > 0.05$) (Table 1).

There were significant differences in PAED Scores [13.00 (7.75), 10.00 (6.00), 9.00 (4.00), 9.00 (2.00), $p = 0.002$], Watcha scores [3.00 (1.00), 3.00 (1.00), 2.00 (1.00), 2.00 (1.00), $p < 0.001$], the occurrence of postoperative EA [25 (62.5%), 21 (56.8.8%), 10 (25.6%), 7 (18.9%), $p < 0.001$], and severe postoperative EA [20 (50.0%), 11 (29.7%), 4 (10.3%), 3 (8.1%), $p < 0.001$] among the groups k_0 , k_1 , k_3 and k_5 . Compared with children in the group k_0 and group k_1 , PAED scores, Watcha scores, incidence of postoperative EA, and severe EA were significantly reduced in the group k_3 , and group k_5 ($p < 0.05$), as shown in Table 2.

There were no significant differences in Ramsay scores before esketamine administration, operation time, duration of anesthesia, postoperative analgesia needs, use of antiemetic drugs, or residence time in the PACU among the four groups ($p > 0.05$). There were significant differences in Ramsay scores after administration, remifentanyl consumption, postoperative FLACC scores, the occurrence of PONV, and the time of tracheal catheter removal among the four groups of patients ($p < 0.05$), as shown in Table 3.

There were significant differences in HR and MAP among the groups at T_3 , T_4 , T_5 and T_6 ($p < 0.05$) (Figure 2).

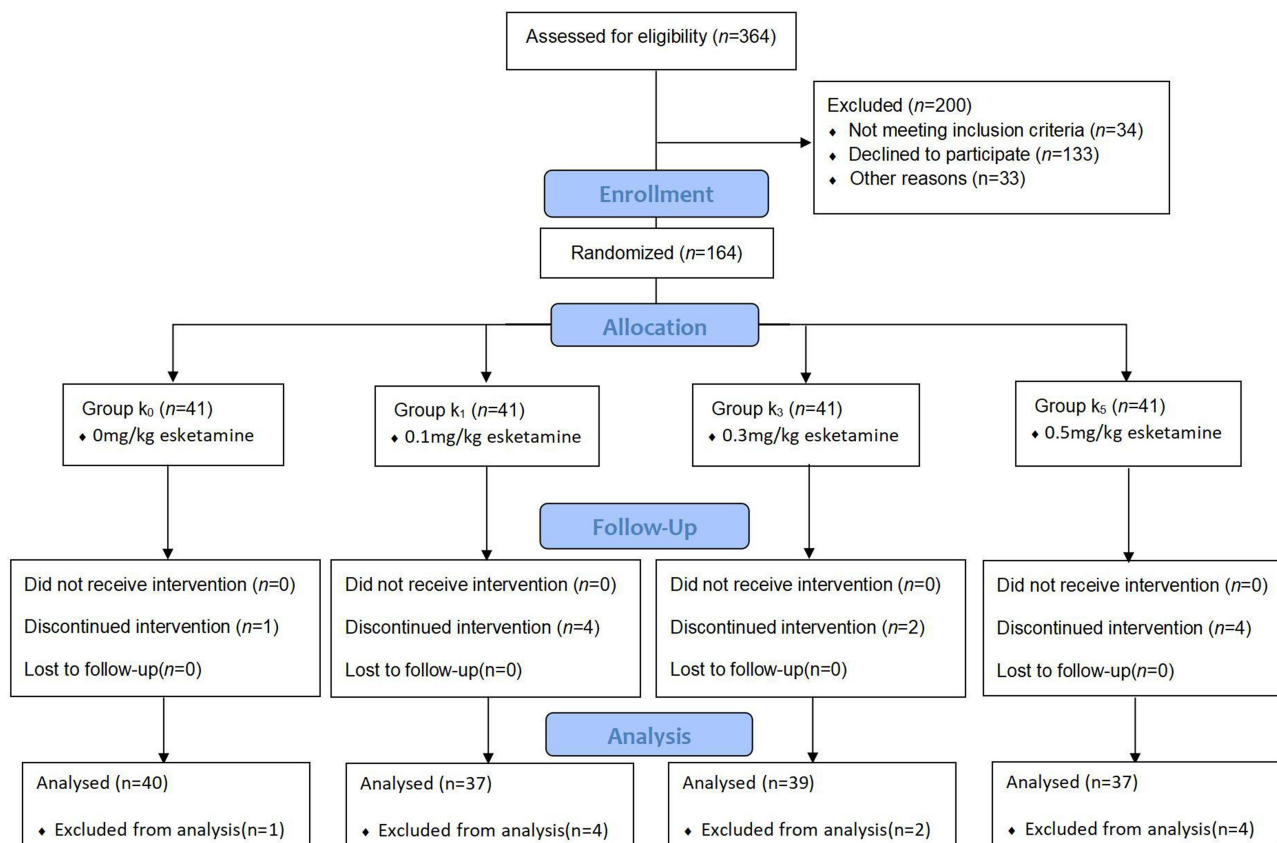


Figure 1 CONSORT flow diagram.
Abbreviation: CONSORT, Consolidated Standards of Reporting Trials.

However, no complications such as somnolence, oxygen desaturation, or respiratory depression occurred during the study period. There were no episodes of hallucinations or bad dreams among the four groups, and all children were discharged 24 hours after surgery.

Table 1 Demographic Characteristics for Four Groups

	Group k ₀ (n=40)	Group k ₁ (n=37)	Group k ₃ (n=39)	Group k ₅ (n=37)	F/χ ²	p
Age (y)	6.68±2.47	7.59±2.36	6.64±2.12	7.46±2.12	1.879	0.136
Sex (M/F)	18/22	20/17	20/19	26/11	5.331	0.149
Height (cm)	119.93±12.63	122.43±13.62	123.59±14.88	125.19±15.51	0.945	0.420
Weight (kg)	29.98±9.61	28.54±7.38	29.05±8.53	29.80±9.88	0.215	0.886
BMI (kg/m ²)	21.41±8.14	19.05±3.85	19.52±6.58	19.39±7.23	0.893	0.449
ASA (I/II)	21/19	14/23	13/26	14/23	3.439	0.329

Notes: Data are presented as the mean ± SD or as the number of patients, as appropriate. *p* < 0.05 was considered statistically significant.
Abbreviations: M, male; F, female; BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 The PAED Scores, Watcha Scores, Incidence of EA and Severe EA

	Group k ₀ (n=40)	Group k ₁ (n=37)	Group k ₃ (n=39)	Group k ₅ (n=37)	H/ χ^2	p
PAED scales	13.00(7.75)	10.00(6.00)	9.00(4.00) ^a	9.00(2.00) ^a	14.406	0.002
Watcha scales	3.00(1.00)	3.00(1.00)	2.00(1.00) ^{ab}	2.00(1.00) ^{ab}	23.007	<0.001
Postoperative EA	25(62.5%)	21(56.8%)	10(25.6%) ^{ab}	7(18.9%) ^{ab}	18.591	<0.001
Severe postoperative EA	20(50.0%)	11(29.7%)	4(10.3%) ^{ab}	3(8.1%) ^{ab}	24.299	<0.001

Notes: Data are presented as M(IQR) or number (%). $p < 0.05$ was considered statistically significant. ^a $p < 0.05$ compared with group k₀, ^b $p < 0.05$ compared with group k₁.

Abbreviations: EA, emergence agitation; PAED scale, Pediatric Anesthesia Emergence Delirium scale; Watcha scale, a 4-point scale to evaluate EA.

Table 3 Intraoperative and Postoperative Data

	Group k ₀ (n=40)	Group k ₁ (n=37)	Group k ₃ (n=39)	Group k ₅ (n=37)	F/ χ^2 /H	p
Before sedation Ramsay scores	1.00(1.00)	2.00(1.00)	1.00(1.00)	1.00(1.00)	2.095	0.553
After sedation Ramsay scores	1.00(1.00)	2.00(1.00)	3.00(1.00) ^{ab}	5.00(0.00) ^{abc}	120.525	<0.001
Remifentanyl consumption (μ g)	309.13 \pm 94.39	284.32 \pm 85.94	246.41 \pm 93.29 ^a	186.89 \pm 98.96 ^{abc}	12.353	<0.001
Postoperative FLACC scores	2.38 \pm 0.84	2.35 \pm 0.92	2.36 \pm 0.84	1.68 \pm 0.78 ^{abc}	6.146	<0.001
Postoperative analgesic need	4(10.0%)	4(10.8%)	4(10.3%)	0(0.0%)	5.018	0.161
The occurrence of PONV	21(52.5%)	18(48.6%)	12(30.8%)	6(16.2%) ^{ab}	13.740	0.003
Use antiemetics	4(10.0%)	2(5.4%)	0(0.0%)	0(0.0%)	5.939	0.052
Time of operation (min)	33.45 \pm 8.59	33.78 \pm 8.17	33.69 \pm 8.99	35.70 \pm 8.20	0.562	0.641
Duration of anesthesia (min)	48.48 \pm 7.22	49.11 \pm 6.52	50.62 \pm 7.02	50.24 \pm 6.72	0.809	0.491
Time of tracheal catheter removal (min)	21.23 \pm 5.21	22.86 \pm 6.12	23.77 \pm 4.29	25.32 \pm 3.94 ^a	5.237	0.002
Time of residence in PACU (min)	51.88 \pm 5.74	52.03 \pm 5.59	50.00 \pm 6.49	50.89 \pm 5.40	1.013	0.389

Notes: Data are presented as mean \pm SD or number (%) or median (interquartile range). $p < 0.05$ was considered statistically significant. ^a $p < 0.05$ compared with group k₀, ^b $p < 0.05$ compared with group k₁, ^c $p < 0.05$ compared with group k₃.

Abbreviations: FLACC, Face Legs, Activity, Cry, and Consolability behavioral pain assessment tool; PONV, Postoperative nausea and vomiting; PACU, post-anesthesia care unit.

Discussion

Esketamine has been shown to be viable as an adjunct to general anesthesia in pediatric patients undergoing flexible fiberoptic bronchoscopy, reducing anesthetic drug requirements and improving recovery quality during diagnostic airway procedures.²⁵ This study shows that intravenous administration of esketamine at doses of 0 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg before anesthesia induction leads to differences in the PAED score and incidence of EA of children after surgery, but it does not affect the length of hospital stay in the PACU and postoperative discharge time (Tables 2 and 3). Compared with the children in the group k₀ and group k₁, the PAED scores, Watcha scores, incidence of postoperative EA, and postoperative severe EA were significantly reduced in the group k₃ and group k₅. Which is consistent with the conclusions of Wang et al, they noted that esketamine doses in the range of 0.3 mg/kg to 0.7 mg/kg were effective in reducing the occurrence of postoperative EA.²⁶ However, the results of this study showed that there was no statistically significant difference was found between the group k₃ and group k₅ in reducing postoperative agitation. Therefore, in this study, when the dose exceeded 0.3mg/kg, the effect of esketamine on the incidence of EA after tonsillectomy and adenoidectomy in children did not gradually decrease with the increase of the dose.

There are many reasons for agitation after general anesthesia in children, the common ones are postoperative pain, the use of inhalation anesthetics (Such as sevoflurane, desflurane),¹² the anxiety of the child before surgery, hypoxia and airway obstruction, and the mode of surgery.^{2,27,28} EA is a common problem during recovery from general anesthesia in

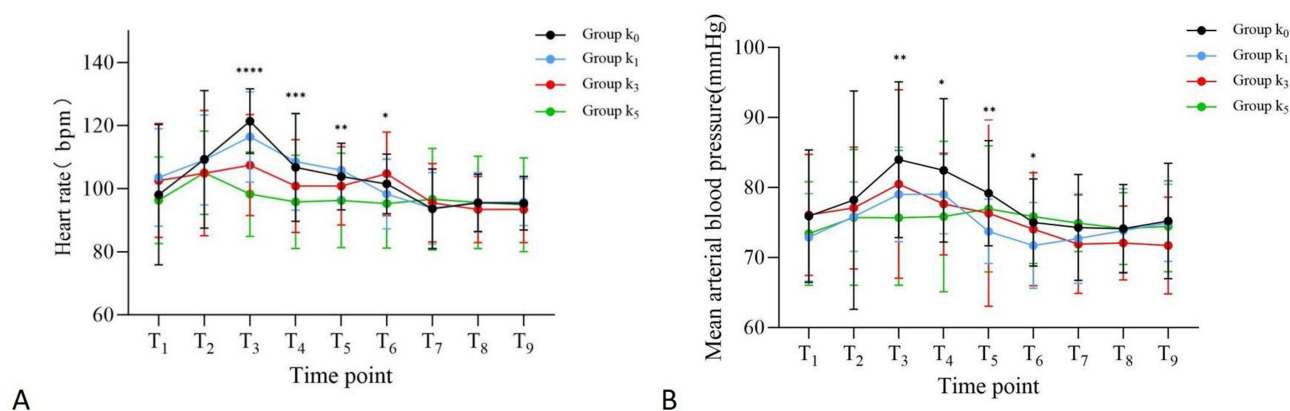


Figure 2 HR and MAP of the four groups at each time point. **(A)** represents the changes in HR at each time point. The comparison of HR at each time point is as follows: T₃, group k₀ vs group k₃ $p < 0.001$, group k₀ vs group k₅ $p < 0.001$, group k₁ vs group k₅ $p < 0.001$, group k₃ vs group k₅ $p = 0.039$; T₄, group k₀ vs group k₅ $p = 0.0182$, group k₁ vs group k₅ $p = 0.003$; T₅, group k₁ vs group k₅ $p = 0.008$. **(B)** represents the changes in MAP at each time point. The comparison of MAP at each time point is as follows: T₃, group k₀ vs group k₅ $p = 0.004$; T₄, group k₀ vs group k₅ $p = 0.036$; T₅, group k₀ vs group k₁ $p = 0.001$; T₆, group k₀ vs group k₅ $p = 0.035$. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; T₁, entering the operating room; T₂, 3 min after administration of esketamine; T₃, after tracheal intubation; T₄, after tracheal catheter removal; T₅, entering PACU; T₆, 5 min after entering PACU; T₇, 10 min after entering PACU; T₈, 15 min after entering PACU; T₉, time of the left PACU.

children, especially after head, neck and maxillofacial surgery.^{12,29} This phenomenon may be driven by age-related neurocognitive vulnerability, postoperative pain from mucosal trauma, airway device irritation, and rapid emergence kinetics of inhalational anesthetics.^{30,31} Due to pharyngeal mucosal nerve exposure, dynamic inflammatory responses and opioid dose limitations in children, the postoperative pain management of most children after tonsillectomy and adenoidectomy is often inadequate.^{32–34} Esketamine exhibits 3–4 times greater affinity for NMDAR than its R-enantiomers and produces sedative, hypnotic, analgesic, and antidepressant effects at low doses,³⁵ it has been shown to reduce postoperative pain in children¹ and reduce the occurrence of EA.¹⁷ In addition, by blocking NMDA receptors, esketamine inhibits the upload of harmful signals, reduces postoperative hyperalgesia and central sensitization,³⁶ Bonaventura et al³⁷ reported that in addition to NMDAR, esketamine also has a moderate affinity for μ -opioid receptors, thereby reducing pain-induced restlessness. This study found that esketamine significantly reduced intraoperative remifentanyl use and postoperative FLACC scores, consistent with Liu¹ and KT's³⁸ study. Li et al¹⁷ showed that 0.2 mg/kg esketamine reduced the incidence of EA in children after tonsillectomy without delaying extubation time and increasing postoperative side effects. Zhou et al used esketamine 0.3 mg/kg in breast and thyroid surgery during anesthesia induction, which reduced the postoperative anxiety and pain scores of patients and promoted the postoperative recovery of patients.³⁹ In this study, esketamine was used before anesthesia induction, and esketamine significantly increased the Ramsay scores during the entry of children, alleviated the preoperative tension of children, and thus played a certain role in reducing the occurrence of postoperative EA in children.

Low-dose esketamine can reduce the incidence of anesthesia-related respiratory depression by increasing ventilatory CO₂ sensitivity.⁴⁰ It can not only reduce the severity of asphyxiation reactions during recovery from general anesthesia, but also ensure a smoother awakening process with fewer adverse effects, leading to a more comfortable awakening period for patients.⁴¹ Liang et al found that 0.3 mg/kg esketamine would not cause adverse reactions such as respiratory depression, hypoxemia, nightmares, hallucinations and insanity in children undergoing laparoscopic surgery, aligning with our findings.³ Song et al mentioned that low doses of esketamine show a good safety profile as it does not increase adverse effects such as dizziness, headache, nausea, vomiting, nightmares, hallucinations, dissociation, the appearance of confusion or hallucinations, and activates the sympathetic nervous system, maintains stable blood pressure and fights respiratory depression.⁴² The results of this study showed that the use of 0.5 mg/kg esketamine before anesthesia induction decreased the postoperative FLACC score and the occurrence of PONV, without increasing the consumption of postoperative analgesics and antiemetics, but extended the time of tracheal catheter withdrawal (Table 3). Therefore, esketamine with a dose higher than 0.5mg/kg may increase the risk of delayed extubation in children. There are potential

age-related differences in esketamine (for example, metabolic variability, susceptibility to psychopathic side effects due to neurodevelopment). It is necessary for future studies to compare the dose-response relationship and safety profiles between pediatric and adult populations.

Esketamine works quickly when administered intravenously, stimulating the sympathetic nerve which increases heart rate and blood pressure.⁴³ Zhao et al found that the use of esketamine could significantly reduce the levels of plasma epinephrine, norepinephrine, and endothelin in patients undergoing cholecystectomy, stabilize hemodynamic responses, and alleviate the stress and inflammatory responses caused by the surgery.¹⁶ This study did not generally find that group k_3 and group k_5 had higher HR and MAP, but there were significant differences in HR and MAP during induction intubation (T_3), tracheal catheter removal (T_4) and the first 5 minutes after entering PACU (T_5 , T_6)(Figure 2). The HR and MAP of children in the group k_0 were significantly higher than those in the other groups, which may be related to the lower dose of esketamine used in this study and the inhibition of the post-tonsillar adenoidectomy stress response. In addition, we discovered an unexpected result that when the esketamine dose were 0.3 mg/kg and 0.5 mg/kg, the injection pain of propofol was significantly relieved, which is consistent with the Su's study, which mentioned that propofol injection pain was significantly reduced when esketamine doses exceeded 0.15 mg/kg.⁴⁴

This study had several limitations. First, studies have shown that the effects of esketamine differ among children of different ages,⁴⁵ and the effect of esketamine on postoperative EA in children of different ages was not observed in this study. Second, in clinical practice, the commonly used dose of esketamine for perioperative sedation and analgesia is 0.1–0.5 mg/kg.⁴⁶ We did not attempt to observe the effect of higher doses of esketamine on postoperative EA, considering that higher doses of esketamine can increase heart rate and blood pressure, and increase the incidence of nausea and visual impairment in children.⁴⁴ Thirdly, the sample size was small, and the study only included Chinese children from a single center. Therefore, larger multicenter and multiethnic cohort studies are warranted.

Conclusions

Intravenous administration of esketamine at dose of 0mg/kg, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg before anesthesia induction leads to differences in the PAED score and incidence of EA of children after adenoidectomy and tonsillectomy. Compared with 0mg/kg and 0.1mg/kg, the effects of 0.3mg /kg and 0.5mg /kg are more significant. Compared with 0.3 mg/kg, 0.5 mg/kg has no significant advantage in reducing postoperative emergence agitation. Therefore, in pediatric anesthesia, 0.3 mg/kg esketamine appears to offer the optimal balance between efficacy and safety in reducing EA.

Abbreviations

EA, emergence agitation; PACU, post-anesthesia care unit; ASA, American Society of Anesthesiologists; NMDAR, N-methyl-D-aspartate receptor; CONSORT, Consolidated Standards of Reporting Trials; BMI, body mass index; ASA, American Society of Anesthesiologists; ECG, electrocardiogram; SPO₂, blood oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RSS, Ramsay sedation scale; Fio₂, oxygen concentration; CO₂, carbon dioxide; MAP, mean arterial blood pressure; PAED, Pediatric Anesthesia Emergence Delirium; FLACC scale, Face, Legs, Activity, Cry, Consolability scale; PONV, postoperative nausea and vomiting; M(IQR), median (interquartile range).

Data Sharing Statement

All data generated or analyzed during this study have been included in the published article. Further inquiries regarding the datasets can be directed to the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Institutional Ethics Committee of the Affiliated Hospital of North Sichuan Medical College, China (approval no. 2023ER270-1), and was registered in the Chinese Clinical Trials.gov (No. ChiCTR2300075038). All the participants provided written informed consent from their parents or legal guardians. This study complied with the Declaration of Helsinki.

Acknowledgments

The authors thank all the nurses, anesthesiologists, and surgeons who participated in this study at the Affiliated Hospital of North Sichuan Medical College.

Disclosure

The authors report no competing interests in this work.

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