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Original Article

Efficacy of esketamine in alleviating emergence delirium and agitation in pediatric patients undergoing adenotonsillectomy under general anesthesia

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Abstract: Objective: To analyze the effect of esketamine on emergence delirium (ED) and emergence agitation (EA) in pediatric patients under general anesthesia. Methods: This retrospective study included 94 pediatric patients who underwent adenotonsillectomy under general anesthesia at General Hospital of Ningxia Medical University from January 2023 to October 2024. The patients were divided into three groups according to different anesthesia protocols they received: Group A (n=30, esketamine 0.5 mg/kg), Group B (n=32, esketamine 0.75 mg/kg), and Group C (n=32, fentanyl 2 μg/kg). Hemodynamic values, surgical indicators, pstoperative pain and agitation (the Face, Legs, Activity, Cry, and Consolability (FLACC) scale face, legs, activity, Cry, and consolability (FLACC) scale and the Pediatric Anesthesia Emergence Delirium (PAED) scale), the incidence of EA and ED, and perioperative adverse events were compared across the groups. Factors associated with EA and ED occurrence were analyzed. Results: Groups A and B exhibited significantly shorter time to spontaneous respiration, extubation, and awakening than Group C (P<0.05). Perioperative heart rate and mean arterial pressure were more stable in Groups A and B (P<0.05). No significant intergroup differences were observed in post-extubation FLACC scores among the groups (P>0.05). However, Group B demonstrated significantly lower PAED scores than both Groups A and C (P<0.05). The incidence of EA and ED was highest in Group C (28.13% and 21.88%, respectively; P<0.05). Group C had higher rates of nausea, vomiting, and excessive airway secretions (P<0.05). Esketamine administration at 0.75 mg/kg significantly reduced the risk of EA (P=0.039) and ED (P=0.043). Conclusion: Compared to fentanyl, esketamine, particularly at a dose of 0.75 mg/kg, eenhanced perioperative hemodynamic stability, reduced postoperative ED and EA incidence, and demonstrated a favorable safety profile in pediatric adenotonsillectomy.

Keywords: Esketamine, emergence delirium, agitation, pediatric patients, adenotonsillectomy

Introduction

Adenotonsillectomy ranks among the most frequently performed pediatric otolaryngology procedures, primarily indicated for adenotonsillar hypertroph [1]. Owing to the unique physiological characteristics of pediatric patients and the specific nature of the surgical site, perioperative management is often challenging. Common complications include intraoperative bleeding, postoperative airway obstruction, and pain, as well as an increased risk of emergence agitation (EA) and emergence delirium (ED) due to pediatric patients' lower pain tolerance [2]. These factors collectively complicate anesthetic management.

Currently, general anesthesia with opioid-based analgesia (e.g., fentanyl) remains the standard approach for adenotonsillectomy. While opioids provide effective analgesia, their use is frequently associated with adverse effects such as respiratory depression, postoperative nausea and vomiting, postoperative delirium and agitation, and an elevated incidence of EA/ED [3]. Reported rates of EA and ED in pediatric adenotonsillectomy range from 20-80% and 10-50%, respectively [4, 5], posing risks for

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postoperative complications and straining clinician-patient rapport.

Esketamine, the S(+) enantiomer of ketamine, has emerged as a promising alternative, offering rapid-onset of action, robust pain control, and minimal respiratory depression. Compared to racemic ketamine, esketamine demonstrates superior analgesic racemic [6]. Recent evidence underscores its utility in diverse surgical contexts, particularly in mitigating EA and ED [7]. Nevertheless, its application in pediatric adenotonsillectomy remains underexplored, with critical gaps in evidence regarding optimal dosing, administration protocols, and comparative efficacy versus conventional opioids. A systematic evaluation of esketamine's dose-dependent effects - especially on EA/ED prevention - is notably lacking.

This study innovatively compares two esketamine doses (0.5 mg/kg and 0.75 mg/kg) against fentanyl, assessing their impacts on perioperative hemodynamics, recovery quality, and postoperative complications. Utilizing validated tools, Consolability (FLACC) scale and the Pediatric Anesthesia Emergence Delirium Scale (PAED) scores, we conducted a thorough analysis of postoperative pain and agitation. Our findings aim to refine anesthetic protocols for pediatric adenotonsillectomy, enhancing both safety and clinical outcomes.

Patients and methods

Case selection

This retrospective study was approved by the Ethics Committee of General Hospital of Ningxia Medical University and conducted in accordance with the principles of the Declaration of Helsinki. The study period spanned from January 2023 to October 2024. A total of 145 pediatric patients were initially identified based on predefined inclusion criteria. A total of 94 out of 145 pediatric patients were included in the final study cohort after screening based on the exclusion criteria. The 94 patients were categorized into three groups based on the anesthetic regimen they received: Group A (n=30, esketamine 0.5 mg/kg), Group B (n=32, esketamine 0.75 mg/kg), and Group C (n=32, fentanyl 2 μg/kg).

Inclusion criteria: (1) American Society of Anesthesiologists (ASA) classification I-II; (2) Age between 3 and 10 years; (3) Normal weight within ±20% of standard weight; (4) Patients who met the diagnostic criteria of adenoid hypertrophy and tonsillar hypertrophy [1] and underwent adenotonsillectomy in General Hospital of Ningxia Medical University.

Exclusion criteria: (1) History of systemic diseases (e.g., congenital heart disease, psychiatric disorders, or innate immune system disorders); (2) Abnormal liver or renal function; (3) Hyperthyroidism; (4) Cardiac conduction block; (5) Intellectual or hearing impairments; (6) Distorted airway anatomy.

Data collection

Data for the selected pediatric patients were obtained through the hospital Healthcare Information Technology (HIT) system.

(1) Baseline characteristics: Age, sex, weight, and ASA classification.

(2) Surgical data: Operative time, anesthesia duration, time to spontaneous respiratory recovery, extubation time, and time to awakening.

(3) Perioperative hemodynamic parameters: A multi-parameter monitor was used to continuously assess perioperative heart rate (HR) and mean arterial pressure (MAP) in pediatric patients. Measurements were recorded at five specific time points: upon admission (T0), after anesthesia induction (T1), at the start of surgery (T2), at the end of surgery (T3), and at extubation (T4). At each time point, three measurements were taken and averaged to minimize measurement error. Variations in HR and MAP reflected the cardiovascular effects of anesthetic agents. Stable hemodynamic values were indicative of better stress response management and safer maintenance of anesthetic depth, thereby contributing to a reduced risk of perioperative cardiovascular complications.

(4) Postoperative pain and agitation: Observation time points were set at 5, 10, and 15 minutes after extubation. The Face, Legs, Activity, Cry, and Consolability (FLACC) scale [8] was used to assess the postoperative pain, evaluating facial expression, leg movement, posture, crying, and consolability, each scored from 0 to 2, with higher scores indicating greater pain. Observations were conducted without

Table 1. Comparison of general data among the three groups

Group	Number of cases	Male/ Female	Age (years)	Weight (kg)	ASA classification (ASA I/ASA II)
Group A	30	16/14	5.8±1.2	22.3±3.4	18/12
Group B	32	17/15	5.6±1.3	21.8±3.6	20/12
Group C	32	18/14	5.9±1.1	22.5±3.3	19/13
F/χ^2	-	0.125	0.438	0.053	0.094
P	-	0.939	0.647	0.949	0.954

Note: ASA: American Society of Anesthesiologists.

interfering with the child's normal activities, evaluating five dimensions: facial expression, leg movement, body posture, crying, and consolability (0-2 points per item), with a total score ranging from 0 to 10. Lower FLACC scores indicated better pain control, contributing to the reduction of physiological stress responses and postoperative anxiety. The Pediatric Anesthesia Emergence Delirium (PAED) scale [9] was used to assess the postoperative agitation. Five items were evaluated: eye contact ability, purposeful movement, awareness of the surrounding environment, level of restlessness, and consolability. Each item was rated on a 0-4 point scale, with the total scores ranging from 0 to 20. Lower PAED scores reflected smoother emergence and more complete cognitive recovery.

(5) Incidence of EA and ED: EA was defined as a FLACC score ≥2, and ED was defined as a PAED score ≥10. Two anesthesiologists independently assessed each case, with discrepancies resolved by a senior anesthesiologist [4].

(6) Perioperative adverse events: The incidence of nausea and vomiting, bradycardia, hypoxemia, and excessive airway secretions was recorded across the three patient groups.

Primary outcome measure: Hemodynamic parameters, FLACC score, PAED score and incidence of EA and ED incidence. Secondary outcome measures: The basic surgical parameters and the occurrence of perioperative adverse event.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY), with two-sided tests and a significance threshold of $P<0.05$. All continuous variables were normally distributed (Shapiro-Wilk test) and were presented as mean ± standard deviation (mean ± SD). One-way ANOVA followed by LSD test was used for comparisons among the three group. Categorical data were expressed as rates and analyzed using the chi-square test or Fisher's exact test, as appropriate. Multivariable logistic regression was conducted to identify potential influencing factors.

Results

Baseline characteristics comparison

There is no significant differences in terms of baseline clinical characteristics, including sex, age, weight, and ASA classification among the three groups ($P>0.05$), indicating good comparability, as presented in **Table 1**.

Surgical parameters comparison

The three groups demonstrated comparable operative times and anesthesia durations (P> 0.05). However, Groups A and B exhibited significantly faster recovery profiles than Group C, with shorter times to spontaneous respiration (P<0.05), earlier extubation (P<0.05), and more rapid return to consciousness (P<0.05), as shown in **Figure 1**.

Hemodynamic parameters comparison

Hemodynamic monitoring revealed that Groups A and B maintained significantly higher heart rate (HR) and mean arterial pressure (MAP) values relative to Group C at all T1, T2, and T3 (P<0.05; **Figure 2**).

Pain assessment (FLACC Scores)

No significant differences in FLACC scores were observed at any postoperative assessment time point (5, 10, and 15 minutes post-extubation) among the groups (all P>0.05; **Figure 3**).

Emergence delirium (PAED scores)

Group B demonstrated significantly lower PAED scores than both Groups A and C at all evalua-

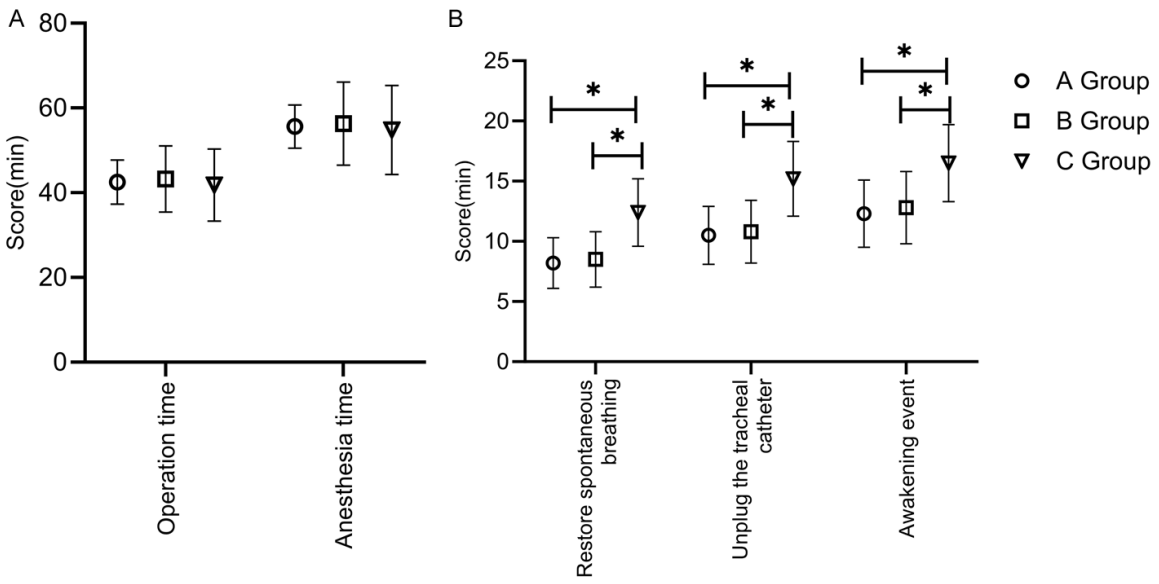

Figure 1. Comparison of surgical timing among the three groups. *P<0.05.

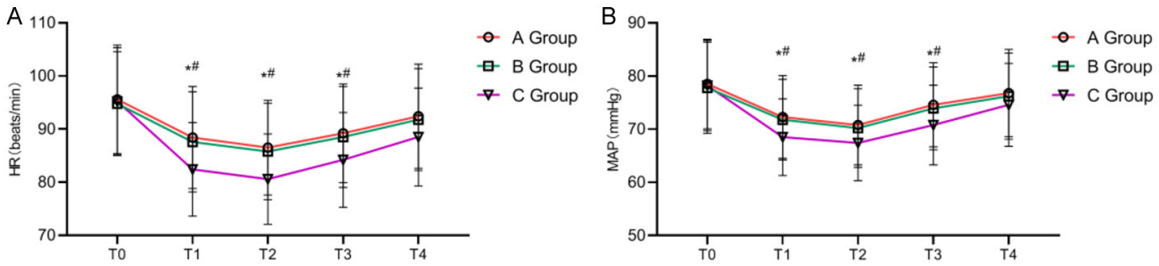

Figure 2. Comparison of perioperative HR and MAP among the three groups. HR: heart rate; MAP: mean arterial pressure. Compared to Group A, *P<0.05; compared to Group B, #P<0.05.

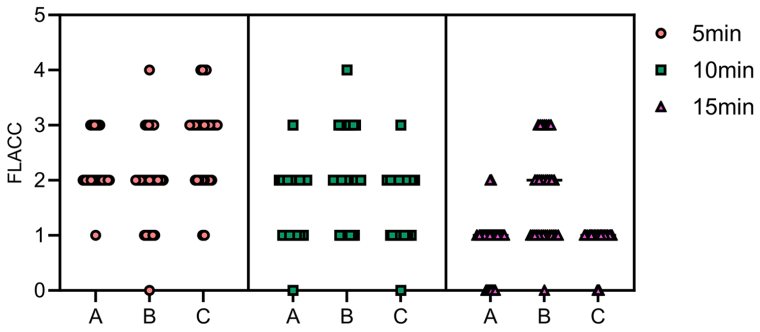

Figure 3. Comparison of FLACC scores at various time points among the three groups. FLACC: The Face, Legs, Activity, Cry, and Consolability scale.

tion time points (5, 10, and 15 minutes post-extubation; all P<0.05), while no significant difference was noted between Groups A and C (P>0.05; **Figure 4**).

Incidence of emergence agitation (EA) and delirium (ED)

Group C showed the highest incidence rates of both EA (28.13%) and ED (21.88%) compared to Groups A and B (both P<0.05; **Table 2**).

Risk factor analysis

The presence or absence of EA and ED in pediatric patients was used as dependent variables, and other factors such as sex, age, and body weight were used as independent variables. The influencing factors for the occurrence of EA and ED were analyzed (**Tables 3**, **4**). Younger age served as an inde-

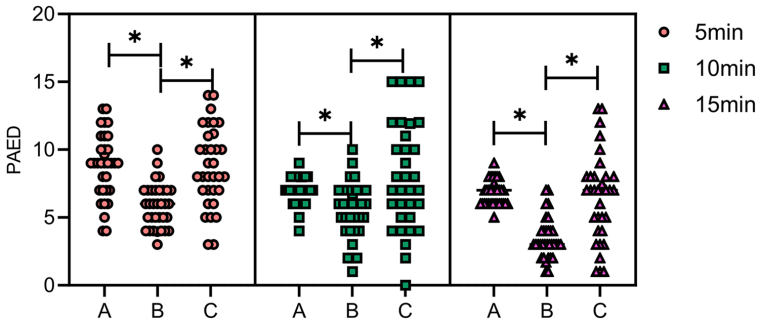

Figure 4. Comparison of PAED scores at various time points among the three groups. PAED: The Pediatric Anesthesia Emergence Delirium scale. *P<0.05.

Table 2. Comparison of the incidence of EA and ED among the three groups [n (%)]

Group	Number of cases	Incidence of EA	Incidence of ED
Group A	30	3 (10.00)	2 (6.67)
Group B	32	2 (6.25)	1 (3.13)
Group C	32	9 (28.13)*,#	7 (21.88)*,#
χ^2		7.8739	7.156
P		0.020	0.028

Note: EA: emergence agitation; ED: emergence delirium. Compared with Group A, *P<0.05; compared with Group B, #P<0.05.

pendent protective factor against both EA (OR=0.43, 95% CI: 0.21-0.82, P=0.012) and ED (OR=0.38, 95% CI: 0.17-0.86, P=0.020). Esketamine administration (0.75 mg/kg) significantly reduced the risk of both EA (OR=0.18, 95% CI: 0.04-0.92, P=0.039) and ED (OR=0.13, 95% CI: 0.02-0.94, P=0.043).

Comparison of perioperative adverse events among the three groups

Group C demonstrated significantly higher rates of perioperative complications, including nausea, vomiting, and excessive airway secretions, compared to Groups A and B (all P<0.05; **Table 5**).

Discussion

This study retrospectively evaluated 94 pediatric patients undergoing adenotonsillectomy under general anesthesia, comparing the effects of two esketamine dose (0.5 mg/kg and 0.75 mg/kg) versus fentanyl (2 μg/kg) in preventing postoperative delirium and agitation. Our findings demonstrate that esketamine administration resulted in significantly faster emergence from anesthesia, improved hemodynamic stability, and reduced incidence of postoperative agitation and delirium compared to fentanyl. Notably, the higher esketamine dose (0.75 mg/kg) showed superior performance in lowering PAED scores, suggesting enhanced protection against emergence delirium.

In terms of recovery quality from anesthesia, our study demonstrated significantly faster return of spontaneous respiration, earlier extubation, and quicker emergence from anesthesia in pediatric patients receiving esketamine compared to fentanyl. These findings align with existing literature on esketamine's pharmacological advantages. Wang et al. [10] reported similar benefits in their study of 60 pediatric patients, where intranasal esketamine combined with oral midazolam yielded rapid sedation onset (43.7±6.9 min) and recovery (89.4±19.5 min), albeit with occasional transient hypertension and tachycardia (8.3% incidence of nausea/vomiting). Complementary evidence from Li et al.'s [11] colonoscopy study (n=150) further supports esketamine's superior recovery profile, showing significantly higher patient and endoscopist satisfaction scores compared to propofol, along with improved hemodynamic stability and reduced awakening time. We hypothesize that esketamine's favorable pharmacokinetic profile underlies these clinical advantages. As the pharmacologically active S(+) enantiomer of ketamine, esketamine demonstrates approximately 4-fold greater NMDA receptor affinity, reduced respiratory depression compared to opioids, and more efficient elimination due to less active metabolites [12]. These properties collectively contribute to its ability to promote faster, more stable recovery from general anesthesia in pediatric populations.

Our results demonstrated superior hemodynamic stability in esketamine-treated patients, with significantly attenuated perioperative fluctuations in cardiovascular measurements compared to the fentanyl group. These clinical

Table 3. Analysis of factors influencing the occurrence of EA in pediatric patients

Variable	Univariate analysis			Multivariable logistic regression analysis		
	Presence of EA (n=14)	Absence of EA (n=80)	*P*	OR	95% CI	*P*
Age (years)	4.28±0.96	5.97±1.18	0.007	0.43	0.21-0.82	0.012
Sex (male/female)	8/6	43/37	0.823			
Body weight (kg)	20.31±2.87	22.32±3.25	0.031	0.86	0.69-1.07	0.175
ASA classification (I/II)	6/8	51/29	0.048	2.58	0.78-8.55	0.121
Operative time (min)	62.54±15.33	56.87±13.12	0.148			
Anesthesia duration (min)	79.68±18.47	72.35±15.26	0.123			
Group A	3 (21.4%)	27 (33.8%)		0.31	0.07-1.45	0.136
Group B	2 (14.3%)	30 (37.5%)		0.18	0.04-0.92	0.039
Group C	9 (64.3%)	23 (28.7%)		Reference group		

Note: ASA: American Society of Anesthesiologists; EA: emergence agitation; OR: odd ratio; 95% CI: 95% confidence interval.

Table 4. Analysis of factors influencing the occurrence of ED in pediatric patients

Variable	Univariate analysis			Multivariable logistic regression analysis		
	Presence of ED (n=10)	Absence of ED (n=84)	*P*	OR	95% CI	*P*
Age (years)	4.05±0.83	5.92±1.22	0.003	0.38	0.17-0.86	0.020
Sex (male/female)	6/4	45/39	0.641			
Body weight (kg)	19.86±2.65	22.26±3.23	0.024	0.91	0.72-1.15	0.418
ASA classification (I/II)	4/6	53/31	0.039	2.84	0.76-10.63	0.119
Operative time (min)	64.37±16.21	57.06±13.09	0.125			
Anesthesia duration (min)	81.25±19.33	72.63±15.42	0.103			
Group A	2 (20.0%)	28 (33.3%)		0.27	0.05-1.54	0.140
Group B	1 (10.0%)	31 (36.9%)		0.13	0.02-0.94	0.043
Group C	7 (70.0%)	25 (29.8%)		Reference group		

Note: ASA: American Society of Anesthesiologists; ED: emergence delirium; OR: odd ratio; 95% CI: 95% confidence interval.

Table 5. Comparison of perioperative adverse events among the three groups [n (%)]

Group	Number of cases	Nausea and vomiting	Bradycardia	Hypoxemia	Excessive airway secretions
Group A	30	2 (6.7)	1 (3.3)	1 (3.3)	2 (6.7)
Group B	32	3 (9.4)	1 (3.1)	1 (3.1)	3 (9.4)
Group C	32	8 (25.0)$^{*,\#}$	3 (9.4)	3 (9.4)	7 (21.9)$^{*,\#}$
χ^2		6.101	1.651	1.651	4.264
P		0.047	0.438	0.438	0.039

Note: Compared to Groups A and B, $^{*}P<0.05$; Compared to Group B, $^{\#}P<0.05$.

observations corroborate the findings of Zheng et al. [13], who reported more stable heart rate and blood pressure profiles using a propofol-esketamine combination (versus propofol-saline) in 104 obese patients undergoing painless gastroscopy, along with reduced incidence of injection pain and hypoxemia. The hemodynamic stabilizing effects of esketamine appear to stem from its multifaceted pharmacologic actions. First, unlike opioids that typically induce marked bradycardia, esketamine provides balanced sympathetic regulation [14]. Second, as a potent NMDA receptor antagonist, esketamine suppresses excessive stress responses triggered by surgical stimuli [14]. Third, Mion et al. [15] elucidated that esketamine modulate calcium channels in vascular smooth muscle, promoting more stable peripheral vascular resistance. Notably, esketamine exhibits weaker inhibitory effects on the cholinergic system than conven-

tional anesthetics, which may partially explain its lower incidence of postoperative cognitive dysfunction.

Our study revealed that 0.75 mg/kg esketamine significantly reduced both PAED scores and the incidence of emergence EA and ED compared to lower-dose esketamine and fentanyl. These findings align with emerging clinical evidence demonstrating esketamine's neuroprotective properties. For example, Liu et al. [16] demonstrated in gastrointestinal surgery patients that esketamine supplementation reduced postoperative pain score, attenuated inflammatory markers at 24 and 48 hours postoperatively, and decreased delirium incidence compared to sufentanil alone. Ron et al. [17] suggested that factors such as age and psychosocial elements may be closely associated with the development of perioperative neurocognitive disorders. Preventive strategies include cognitive preadaptation, perioperative assessment, multidisciplinary care, and multimodal analgesia. Among these strategies, esketamine has shown efficacy in reducing the incidence of postoperative delirium and is therefore recommended. Evidence from clinical experience and literature suggests that esketamine may help stabilize postoperative cognitive function in pediatric patients by modulating NMDA receptors [18]. Furthermore, esketamine provides superior analgesic effects with reduced respiratory depression compared to fentanyl, thereby reducing postoperative stress responses [19, 20]. Esketamine may also enhance early postoperative cognitive function by modulating hippocampal neuronal plasticity.

Regarding safety outcomes, our findings demonstrated a significantly lower incidence of adverse events such as nausea and vomiting and excessive airway secretions in the esketamine groups compared to the fentanyl group. This clinical advantage is consistent with the findings of Liao et al. [21], who performed a randomized, double-blind controlled trial involving 198 pediatric patients aged 2-5 years and reported that esketamine-dexmedetomidine combination reduced ED risk without increasing the incidence of perioperative complications such as nausea and vomiting, ultimately improving parental satisfaction. To investigate the reasons for the safety advantages of esketamine, we propose that these may stem from its unique pharmacologic properties. First, esketamine has a markedly less disruptive effect on gastrointestinal smooth muscle activity and digestive secretory function compared to fentanyl, thereby reducing the risk of postoperative gastrointestinal adverse events [22]. Moreover, esketamine exerts a protective effect on upper airway reflexes, which better preserves pharyngeal protective reflexes in the early postoperative period and lowers the risk of aspiration of secretions. This is particularly critical in pediatric procedures involving the upper airway, such as tonsillectomy and adenoidectomy [23]. Collectively, these mechanisms contribute to the superior safety profile of esketamine in pediatric patients undergoing adenotonsillectomy.

To date, no studies had compared the effects of different esketamine doses in pediatric patients undergoing adenotonsillectomy. However, a related study in elderly patients undergoing gastrointestinal surgery [24] showed that continuous infusion of esketamine at 0.125 mg/kg/h significantly reduced the incidence of delirium, improved intraoperative hemodynamic parameters and bispectral index values, and lowered the incidence of cardiovascular adverse events. In the present study, a controlled comparison revealed that a 0.75 mg/kg dosage was associated with a lower incidence of postoperative agitation and delirium in pediatric patients, without a significant increase in adverse effects such as nausea and vomiting. These findings provide a valuable reference for future individualized esketamine dosage selection in clinical practice.

This study was the first to compare systematically the effects of two different doses of esketamine (0.5 mg/kg and 0.75 mg/kg) with conventional fentanyl in pediatric adenotonsillectomy. It addressed a gap in current research on optimal esketamine dosing and provided a more precise reference for individualized clinical application. However, this study has several notable limitations, including its single-center, retrospective design and the lack of long-term follow-up, both of which may have introduced bias into the findings. To address these limitations, a large-scale, multi-center, prospective randomized controlled trial with extended fol-

low-up is planned to further validate individualized esketamine dosing strategies.

Conclusion

Esketamine emerged as an effective and safe analgesic option for pediatric adenotonsillectomy. Compared to fentanyl, esketamine demonstrated superior perioperative hemodynamic stability, significantly lower incidence of postoperative emergence ED and EA, and an improved safety profile with fewer adverse effects. Notably, the 0.75 mg/kg dose of esketamine showed enhanced efficacy over 0.5 mg/kg, suggesting its potential as more proper dosage for minimizing perioperative neurobehavioral disturbances in this population. These findings support the incorporation of esketamine, particularly at 0.75 mg/kg, into clinical practice for pediatric airway surgery.

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Disclosure of conflict of interest

None.

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References

[1] Kaditis AG and Gozal D. Adenotonsillectomy: the good, the bad and the unknown. Curr Opin Pulm Med 2022; 28: 537-542.

[2] Ishman SL, Maturo S, Schwartz S, McKenna M, Baldassari CM, Bergeron M, Chernobilsky B, Ehsan Z, Gagnon L, Liu YC, Smith DF, Stanley J, Zalzal H and Dhepyasuwan N. Expert consensus statement: management of pediatric persistent obstructive sleep apnea after adenotonsillectomy. Otolaryngol Head Neck Surg 2023; 168: 115-130.

[3] Jaensch SL, Cheng AT and Waters KA. Adenotonsillectomy for obstructive sleep apnea in children. Otolaryngol Clin North Am 2024; 57: 407-419.

[4] He J, Zhang L, Tao T, Wen X, Chen D, Zheng X, Luo C, Liang H and Wang H. Nalbuphine reduces the incidence of emergence agitation in children undergoing adenotonsillectomy: a prospective, randomized, double-blind, multicenter study. J Clin Anesth 2023; 85: 111044.

[5] Hazkani I, Billings KR and Thompson DM. Adenotonsillectomy or watchful waiting for pediatric sleep-disordered breathing. JAMA 2023; 330: 2057-2058.

[6] Nikayin S, Murphy E, Krystal JH and Wilkinson ST. Long-term safety of ketamine and esketamine in treatment of depression. Expert Opin Drug Saf 2022; 21: 777-787.

[7] Feeney A and Papakostas GI. Pharmacotherapy: ketamine and esketamine. Psychiatr Clin North Am 2023; 46: 277-290.

[8] Danisan G and Taydas O. Ultrasound-guided subgluteal sciatic nerve block for pain management during endovascular treatment for below-the-knee arterial occlusions. J Vasc Interv Radiol 2022; 33: 279-285.

[9] Yang X, Lin C, Chen S, Huang Y, Cheng Q and Yao Y. Remimazolam for the prevention of emergence delirium in children following tonsillectomy and adenoidectomy under sevoflurane anesthesia: a randomized controlled study. Drug Des Devel Ther 2022; 16: 3413-3420.

[10] Wang J, Zeng J, Zhao N, Chen S, Chen Z, Liao J, Ran H and Yu C. Intranasal esketamine combined with oral midazolam provides adequate sedation for outpatient pediatric dental procedures: a prospective cohort study. Int J Surg 2023; 109: 1893-1899.

[11] Li W, Zhao J, Hao R, Wang S, Chen M, Liu H, Qi L and Hao Z. The efficacy and safety of remimazolam besylate combined with esketamine for outpatient colonoscopy: a prospective, randomized, controlled clinical trial. Drug Des Devel Ther 2023; 17: 2875-2887.

[12] Zhan Y, Liang S, Yang Z, Luo Q, Li S, Li J, Liang Z and Li Y. Efficacy and safety of subanesthetic doses of esketamine combined with propofol in painless gastrointestinal endoscopy: a prospective, double-blind, randomized controlled trial. BMC Gastroenterol 2022; 22: 391.

[13] Zheng L, Wang Y, Ma Q, Liang W, Zhang X, Ren Z, Qin W, Meng F, Li Y, Fan G and Yin N. Efficacy and safety of a subanesthetic dose of esketamine combined with propofol in patients with obesity undergoing painless gastroscopy: a prospective, double-blind, randomized controlled trial. Drug Des Devel Ther 2023; 17: 1347-1356.

[14] Xu LL, Wang C, Deng CM, Dai SB, Zhou Q, Peng YB, Shou HY, Han YQ, Yu J, Liu CH, Xia F, Zhang SQ, Wang DX and Chen XZ. Efficacy and safety of esketamine for supplemental analgesia during elective cesarean delivery: a randomized clinical trial. JAMA Netw Open 2023; 6: e239321.

[15] Mion G and Himmelseher S. Esketamine: less drowsiness, more analgesia. Anesth Analg 2024; 139: 78-91.
[16] Liu J, Wang T, Song J and Cao L. Effect of esketamine on postoperative analgesia and postoperative delirium in elderly patients undergoing gastrointestinal surgery. BMC Anesthesiol 2024; 24: 46.
[17] Ron D and Deiner S. Postoperative delirium and neurocognitive disorders: updates for providers caring for cancer patients. Curr Oncol Rep 2024; 26: 1176-1187.
[18] Wang H, Te R, Zhang J, Su Y, Zhou H, Guo N, Chi D and Huang W. Effects of a single subanesthetic dose of esketamine on postoperative subthreshold depressive symptoms in patients undergoing unilateral modified radical mastectomy: a randomised, controlled, double-blind trial. BMC Psychiatry 2024; 24: 315.
[19] Xiong X, Shao Y, Chen D, Chen B, Lan X and Shi J. Effect of esketamine on postoperative delirium in patients undergoing cardiac valve replacement with cardiopulmonary bypass: a randomized controlled trial. Anesth Analg 2024; 139: 743-753.
[20] Yang Y, Zhang Y, Zhou G, Yang Z, Yan H and Zhang J. Efficacy of epidural esketamine on postoperative sleep quality after laparoscopic and robotic lower abdominal surgeries: a study protocol for randomised, double-blind, controlled trial. BMJ Open 2024; 14: e081589.
[21] Liao Y, Xie S, Zhuo Y, Chen S, Luo Y, Wei Y and Yao Y. Intranasal dexmedetomidine-esketamine combination premedication versus monotherapy for reducing emergence delirium and postoperative behavioral changes in pediatric tonsillectomy and/or adenoidectomy: a randomized controlled trial. Drug Des Devel Ther 2024; 18: 4693-4703.
[22] Lu Y, Yin G, Jin C, Gu K, Bao D, Xu W and Yang Z. The application value of esketamine and dexmedetomidine in preventing postoperative delirium and hyperalgesia in elderly patients with thoracic anesthesia. Altern Ther Health Med 2024; 30: 80-85.
[23] Chen S, Yang JJ, Zhang Y, Lei L, Qiu D, Lv HM, Sun ZT, Hashimoto K and Yang JJ. Risk of esketamine anesthesia on the emergence delirium in preschool children after minor surgery: a prospective observational clinical study. Eur Arch Psychiatry Clin Neurosci 2024; 274: 767-775.
[24] Ma J, Wang F, Wang J, Wang P, Dou X, Yao S and Lin Y. The effect of low-dose esketamine on postoperative neurocognitive dysfunction in elderly patients undergoing general anesthesia for gastrointestinal tumors: a randomized controlled trial. Drug Des Devel Ther 2023; 17: 1945-1957.