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Original Article

Association of esketamine anesthetic induction with emergence agitation in children undergoing adenoidectomy: a mediation analysis of early postoperative pain

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Abstract: Objectives: To evaluate the association between documented induction esketamine use and emergence agitation in children undergoing adenoidectomy, and to quantify the extent to which early postoperative pain statistically mediates this association. Methods: This single-center retrospective cross-sectional study included 240 children undergoing adenoidectomy under sevoflurane anesthesia. Children were grouped by documented induction esketamine (0.3 mg/kg) use. Emergence agitation was defined as a Pediatric Anesthesia Emergence Delirium (PAED) score ≥10 within 30 minutes of post-anesthesia care unit (PACU) arrival. The peak Face, Legs, Activity, Cry, Consolability (FLACC) score was the prespecified mediator. We performed regression, mediation, subgroup, and sensitivity analyses. Results: Emergence agitation occurred in 41 (34.2%) children without esketamine and 22/120 (18.3%) with esketamine (χ^2 = 7.77, P = 0.005). Esketamine was associated with lower odds of emergence agitation (OR 0.46, 95% CI 0.25-0.83, P = 0.011), lower peak PAED (MD -1.88, P<0.001), lower peak FLACC (MD -1.15, P<0.001), and less rescue analgesia (OR 0.48, P = 0.037). Extubation time and PACU stay were similar. Mediation analysis indicated a significant indirect pathway through early pain, accounting for 27.2% of the total association (P = 0.002). Exploratory follow-up showed no significant between-group differences, but validated scales and chronic pain outcomes were unavailable. Conclusions: Documented induction esketamine use was associated with less emergence agitation and lower early pain after adenoidectomy. These findings indicate non-causal statistical pathway evidence. They neither verify an N-methyl-D-aspartate-receptor mechanism nor establish an optimal dose. Prospective dose-ranging trials and validated longitudinal assessments are required.

Keywords: Esketamine, emergence agitation, adenoidectomy, pediatric anesthesia, postoperative pain, statistical pathway analysis, long-term recovery

Introduction

Emergence agitation and emergence delirium are common complications during recovery from pediatric general anesthesia, particularly in otorhinolaryngologic surgery. A recent systematic review and meta-analysis of 16 studies including 9,598 children reported a pooled emergence delirium prevalence of 19.2% (95% CI 0.12 to 0.29). Younger age was associated with higher prevalence, and head and neck surgery with greater risk (OR 2.34, 95% CI 1.29 to 4.27) [1]. Clinical reviews have emphasized that this state is characterized by inconsolability, non-purposeful movement, and impaired awareness of the environment. It causes distress to caregivers and staff and may increase the risk of self-injury, accidental line removal, and disruption of postoperative care [2-4]. Adenoidectomy is a particularly relevant context because children awaken rapidly after short volatile anesthetics, often with throat discomfort, airway irritation, and unfamiliar surroundings, and they may experience parental separation during early recovery.

Assessing emergence agitation in children is challenging because delirium-like behaviors and pain-related distress partially overlap. The Pediatric Anesthesia Emergence Delirium

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(PAED) scale was developed to measure this condition and remains one of the most widely used instruments in pediatric anesthesia research [5]. However, comparative studies have shown that different PAED cutoffs can produce different incidence estimates, supporting the need for prespecified diagnostic criteria [6]. Pain tools such as the Face, Legs, Activity, Cry, Consolability (FLACC) scale are commonly used in young children who may not reliably verbalize pain. The original FLACC validation study concluded that it provides a practical behavioral framework for quantifying postoperative pain [7]. A retrospective analysis further showed that pain and delirium behaviors frequently cooccur after anesthesia, and that using both PAED and pain assessments can help differentiate pain-predominant agitation from delirium-predominant agitation [8]. Similarly, a prospective observational study by Somaini and colleagues concluded that while validated tools are helpful, they do not fully eliminate the diagnostic challenge of distinguishing emergence delirium from pain [9].

Esketamine, the S-enantiomer of ketamine, is increasingly used as an adjunct in pediatric anesthesia. It provides analgesia, reduces central sensitization through N-methyl-D-aspartate (NMDA)-receptor antagonism, and may attenuate perioperative opioid requirements while preserving respiratory drive at subanesthetic doses. In a randomized study of 80 children undergoing tonsillectomy, Li and colleagues reported that low-dose esketamine reduced the incidence of emergence agitation from 27.5% in the control group to 5.0% in the esketamine group, with a longer time to eye opening but no significant prolongation of extubation or post-anesthesia care unit (PACU) discharge time [10]. In another randomized study of 108 preschool children undergoing tonsillectomy and/or adenoidectomy, Chen and colleagues found that S-ketamine 0.2 mg/kg given at the end of anesthesia reduced the proportion of children with an Aono score ≥3 (7% vs. 22%) and lowered pain scores (median 4 vs. 6), without increasing extubation time or adverse events [11]. More recently, a dose-comparison randomized study of 164 children undergoing tonsillectomy and adenoidectomy reported emergence agitation rates of 62.5%, 56.8%, 25.6%, and 18.9% in the 0, 0.1, 0.3, and 0.5 mg/kg esketamine groups, respectively, suggesting that 0.3 mg/kg may provide a favorable balance between anti-agitation benefit and recovery profile [12].

Despite these advances, two clinically important questions remain unresolved. First, most evidence evaluates esketamine administered at the end of surgery or as premedication, whereas less real-world evidence focuses specifically on documented administration during induction for children undergoing adenoidectomy alone. Second, although esketamine appears to be related to both emergence agitation and early postoperative pain, the degree to which its anti-agitation association is statistically transmitted through pain reduction has rarely been quantified. This distinction is clinically important: an association pattern operating largely through pain relief would support explicit pain-centered recovery pathways, whereas a residual association independent of measured pain would suggest additional sedative, dissociative, anxiolytic, or arousal-modulating pathways. Therefore, this study aimed to evaluate the association between documented esketamine use during induction and emergence agitation in children undergoing adenoidectomy, and to quantify whether early pain statistically mediated this association. Because the design was retrospective and observational, all pathway estimates were prespecified as statistical mediation rather than causal or molecular-mechanistic proof. This analysis was not designed to verify an NMDA-receptor pathway experimentally, estimate a dose-response relationship, nor quantify long-term outcomes with validated prospective instruments; these remain explicit evidence gaps.

Methodology

Study design and participants

We conducted a single-center, retrospective cross-sectional study at Tangshan Maternal and Child Health Hospital, Hebei, China, covering the period from April 1, 2023, to December 31, 2024. The analytic dataset was compiled at the child-level by integrating retrospective perioperative anesthesia records, PACU assessments, nursing documentation, and routine follow-up forms. Anesthesia and PACU nurses completed standardized PAED and FLACC assessment forms as part of routine clinical

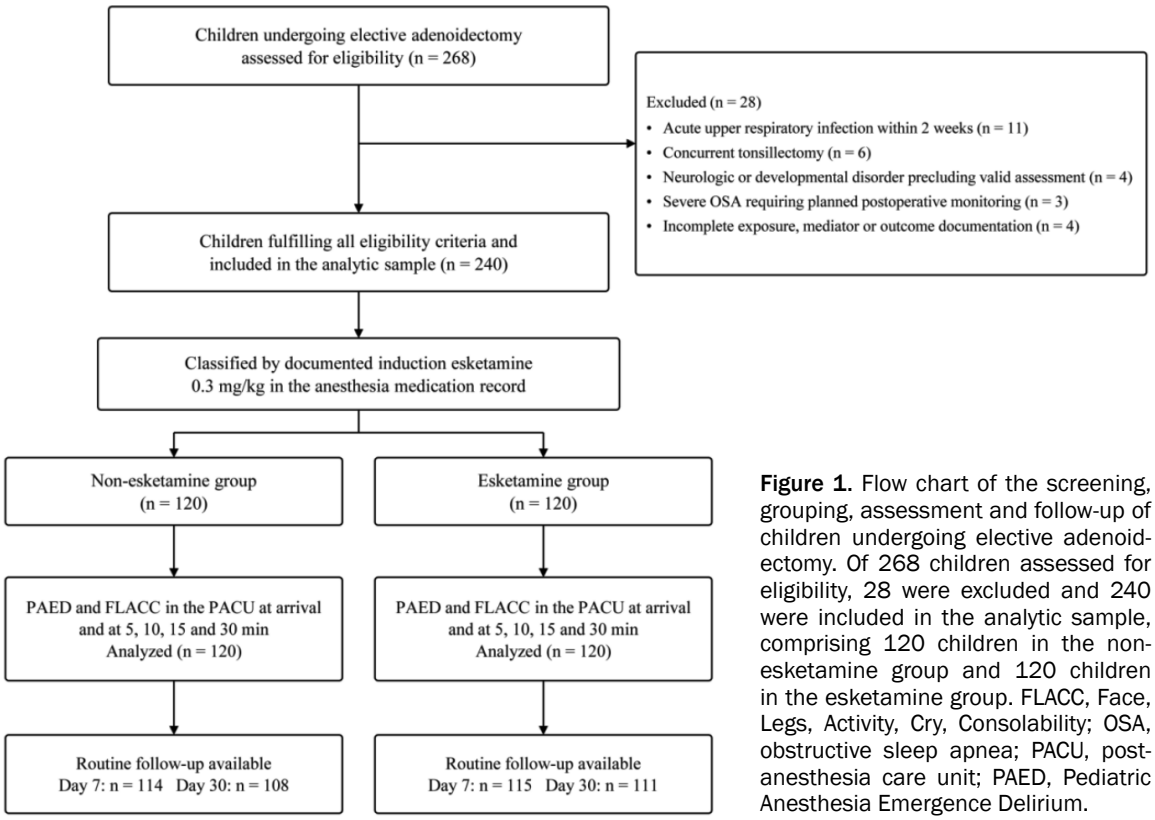

Figure 1. Flow chart of the screening, grouping, assessment and follow-up of children undergoing elective adenoidectomy. Of 268 children assessed for eligibility, 28 were excluded and 240 were included in the analytic sample, comprising 120 children in the non-esketamine group and 120 children in the esketamine group. FLACC, Face, Legs, Activity, Cry, Consolability; OSA, obstructive sleep apnea; PACU, post-anesthesia care unit; PAED, Pediatric Anesthesia Emergence Delirium.

documentation. A second reviewer randomly re-checked a subset of case-report forms against source records, and any discrepancies were resolved through consensus with a senior anesthesiologist.

The study protocol was reviewed and approved by the institutional ethics committee of Tangshan Maternal and Child Health Hospital (IRB No.: 2023-041-01). Because this retrospective cross-sectional analysis used de-identified routine records and involved no additional patient contact or study-specific procedure, the committee waived the requirement for individual informed consent. We de-identified all study data before analysis and stored them on password-protected institutional systems in accordance with hospital data-governance policies.

Inclusion criteria: (1) Children aged 3-9 years with ASA physical status I or II; (2) Undergoing elective adenoidectomy without concurrent tonsillectomy; (3) With complete documentation of prespecified exposure, mediator, and outcome variables as well as preoperative anxiety status.

Exclusion criteria: (1) Known esketamine allergy or contraindication; (2) Developmental or neurologic disorders precluding valid behavioral assessment; (3) Chronic sedative or analgesic use; (4) Acute upper respiratory infection within 2 weeks pre-operatively; (5) Congenital airway malformation; (6) Severe obstructive sleep apnea (OSA) requiring postoperative intensive monitoring; (7) Significant hepatic, renal, or cardiovascular disease; (8) Concurrent tonsillectomy or any other concomitant airway procedure; (9) Incomplete documentation of the prespecified exposure, mediator, outcome, or covariate variables.

The final analytic sample comprised 240 children (120 in the esketamine group and 120 in the non-esketamine group). The detailed screening process is shown in the flow chart in **Figure 1**.

This was a non-interventional retrospective study with no random allocation; no in vitro, ex vivo, animal, receptor, biomarker, or pharmacokinetic experiments were performed. Accordingly, “mediation” in this manuscript refers

only to statistical decomposition rather than experimental validation of NMDA-receptor or other molecular mechanisms.

The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statements [13, 14]. Eligibility criteria, exposure-outcome definitions, covariate coding, and analytical plans were prespecified prior to data abstraction. No formal sample-size calculation was conducted; all consecutive eligible children within the study window were enrolled. Although the final sample with 63 agitation events afforded sufficient power for the primary multivariable model, mediation, subgroup, follow-up, and rare-event analyses lacked independent power and should be interpreted as exploratory. We focused on the direction, magnitude, and precision of effect estimates instead of confirmatory inference.

Exposure ascertainment and record review

We ascertained exposure status from the intraoperative anesthesia medication record. Children were classified as exposed if the record documented intravenous esketamine 0.3 mg/kg during induction, and as unexposed if no esketamine was documented. To reduce misclassification, two reviewers independently checked anesthesia medication sheets, electronic administration records, and PACU handover notes. Initial agreement was 98.3% (236/240); the four discrepant records were resolved by consensus with a senior anesthesiologist before database lock. The analysts used a deidentified dataset with exposure groups coded numerically until all primary analyses were finalized.

Anesthetic and PACU management

All children fasted according to institutional guidelines and received no routine sedative premedication. Standard monitoring included electrocardiography, pulse oximetry, noninvasive blood pressure, and end-tidal carbon dioxide and sevoflurane concentrations. Preoperative anxiety was assessed using the modified Yale Preoperative Anxiety Scale (mYPAS); a score ≥40 was prespecified as high anxiety for subgroup analyses.

Anesthesia was induced with sevoflurane in oxygen and intravenous propofol 2-3 mg/kg. All children received sufentanil 0.2 μg/kg and rocuronium 0.6 mg/kg before intubation. For children in the esketamine group, esketamine 0.3 mg/kg was administered intravenously over 30 seconds immediately after propofol, whereas children in the non-esketamine group underwent an identical anesthetic regimen without esketamine. Anesthesia was maintained with sevoflurane and remifentanil, titrated to maintain hemodynamic stability and age-appropriate depth. Dexamethasone 0.15 mg/kg and ondansetron 0.1 mg/kg were given for antiemetic prophylaxis, and acetaminophen 15 mg/kg intravenously after adenoid removal.

Only one routine induction regimen of esketamine was identified in medical records. No alternative dose or administration-time groups were available; thus, this dataset cannot support estimation of a dose-response curve, optimal dosing interval, or age- or anxiety-stratified dose recommendations.

At surgery end, neuromuscular blockade was antagonized when indicated, and the trachea was extubated after the child demonstrated adequate spontaneous ventilation, protective reflexes, and hemodynamic stability. Children were transferred to the PACU with standard monitoring.

In the PACU, PAED and FLACC scores were recorded at arrival and at 5, 10, 15, and 30 minutes. When both agitation and pain behaviors were present, nurses were instructed to treat pain first when FLACC was ≥4 (fentanyl 0.5 μg/kg IV) and to reserve propofol 0.5 mg/kg IV rescue for agitation threatening airway safety, self-injury, or wound disruption. This pathway was derived from routine care, not a prospectively validated protocol.

Outcomes and measurements

The primary outcome was emergence agitation during the first 30 minutes after PACU arrival, defined a priori as a PAED score ≥10 at any scheduled assessment. We recorded PAED scores at PACU arrival and at 5, 10, 15, and 30 minutes. We analyzed the peak PAED score during this interval as a continuous secondary outcome. We defined severe emergence agitation as a PAED score ≥12 at any assessment.

The prespecified statistical mediator was early pain intensity, assessed using the FLACC scale during the same 30-minute PACU interval. We recorded FLACC scores at the same time points as PAED scores and retained the peak FLACC score as a continuous mediator for the primary mediation analysis. We defined moderate-to-severe early pain as a FLACC score ≥4. Because exposure, mediator, and outcome data were abstracted from records for the same encounter, we interpret mediation results as statistical pathway evidence rather than proof of a pain mechanism or NMDA-receptor-mediated molecular process.

Additional recovery outcomes included time to eye opening, extubation time, PACU length of stay, rescue analgesia, rescue propofol administration, postoperative nausea or vomiting (PONV), transient oxygen desaturation (SpO2 <94%), laryngospasm, tachycardia requiring clinical management, hypertension requiring clinical management, maximum heart-rate increase from preinduction baseline, maximum mean arterial pressure (MAP) increase from preinduction baseline, hallucination or nightmare reported before PACU discharge, and any other adverse events documented by PACU staff.

We abstracted longer-term outcomes from routine follow-up records at day 7 (±2 days) and day 30 (±5 days), when available. These included caregiver-reported new or worsened negative postoperative behavior, new or worsened sleep disturbance, delayed nausea or vomiting, hallucination or nightmare after discharge, and unplanned medical visits. We defined negative behavior pragmatically as any new or worsened separation anxiety, appetite disturbance, temper tantrum, withdrawal, or regression. We defined sleep disturbance as new or worsened difficulty falling asleep, night waking, or distressing dreams.

The routine follow-up forms consisted of caregiver-reported symptom items rather than prospectively administered validated quantitative instruments. Recurrent agitation after the 30-day assessment and persistent or chronic pain at or beyond 1 month were not systematically recorded and consequently could not be analyzed.

Statistical analysis

Descriptive statistics were presented for the overall sample and by esketamine group. Continuous variables were summarized as mean (standard deviation) when approximately normally distributed and as median (interquartile range) otherwise. Categorical variables were summarized as number (percentage). For between-group comparisons, we used Welch's t-test for approximately normal continuous variables, the Wilcoxon rank-sum test for non-normal continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. In response to reviewer comments, we added test statistics to the tables alongside *P* values; we labeled Fisher's exact comparisons as exact tests because no single chi-square statistic was estimated.

We estimated primary exposure-outcome associations using prespecified regression models with four nested adjustment sets. Model I included only esketamine exposure. Model II additionally adjusted for age, sex, and body weight. Model III additionally adjusted for ASA status, OSA-related symptoms, and preoperative mYPAS score. Model IV, the primary model, additionally adjusted for surgery duration, anesthesia duration, mean end-tidal sevoflurane concentration, and intraoperative remifentanil dose. We analyzed binary outcomes using logistic regression and reported odds ratios (ORs) with 95% confidence intervals (CIs). Continuous outcomes were analyzed using linear regression with heteroskedasticity-consistent robust standard errors and reported mean differences (MDs) with 95% CIs. The primary analysis used the complete analytic sample with available data for all prespecified variables.

Subgroup heterogeneity was evaluated by adding prespecified esketamine-by-subgroup interaction terms to Model IV. Candidate modifiers were child sex, age group (3-5 vs. 6-9 years), high preoperative anxiety, OSA-related symptoms, adenoid hypertrophy grade (II/III vs. IV), and anesthesia duration (<45 vs. ≥45 minutes). We reported subgroup-specific estimates for all candidate modifiers, but we emphasize that these interaction analyses were exploratory because no dedicated power calculation was performed.

Table 1. Baseline and perioperative characteristics of children by documented esketamine exposure

Characteristic	All (n = 240)	Non-esketamine group (n = 120)	Esketamine group (n = 120)	*P* value (test statistic)
Age, years	5.6±1.5	5.6±1.5	5.5±1.4	0.62 (t = 0.50)
Age group 3 to 5 years	132 (55.0)	67 (55.8)	65 (54.2)	0.17 (χ^2 = 0.07)
Age group 6 to 9 years	108 (45.0)	53 (44.2)	55 (45.8)	0.46 (χ^2 = 0.07)
Male sex	155 (64.6)	77 (64.2)	78 (65.0)	0.89 (χ^2 = 0.02)
Body weight, kg	21.1±5.1	20.9±5.2	21.2±5.0	0.65 (t = 0.45)
ASA physical status I	143 (59.6)	72 (60.0)	71 (59.2)	0.90 (χ^2 = 0.02)
ASA physical status II	97 (40.4)	48 (40.0)	49 (40.8)	0.90 (χ^2 = 0.02)
OSA-related symptoms	113 (47.1)	58 (48.3)	55 (45.8)	0.70 (χ^2 = 0.15)
Prior anesthesia exposure	32 (13.3)	15 (12.5)	17 (14.2)	0.70 (χ^2 = 0.15)
mYPAS score	41.0±11.4	41.2±11.5	40.7±11.3	0.73 (t = 0.34)
High preoperative anxiety (mYPAS ≥40)	138 (57.5)	70 (58.3)	68 (56.7)	0.79 (χ^2 = 0.07)
Surgery duration, min	26.2±6.8	25.8±6.7	26.6±6.9	0.36 (t = 0.91)
Anesthesia duration, min	44.1±8.8	43.7±8.6	44.5±9.0	0.48 (t = 0.70)
Mean end-tidal sevoflurane, %	1.51±0.25	1.52±0.26	1.50±0.25	0.54 (t = 0.61)
Remifentanil dose, microgram/kg/min	0.09±0.03	0.09±0.03	0.09±0.03	0.81 (t = 0.24)
Sufentanil induction dose, microgram/kg	0.20±0.04	0.20±0.04	0.20±0.04	0.96 (t = 0.05)
Adenoid hypertrophy grade II	28 (11.7)	15 (12.5)	13 (10.8)	0.35 (χ^2 = 0.22)
Adenoid hypertrophy grade III	126 (52.5)	62 (51.7)	64 (53.3)	0.18 (χ^2 = 0.31)
Adenoid hypertrophy grade IV	86 (35.8)	43 (35.8)	43 (35.8)	0.91 (χ^2 = 0.56)

Values are mean ± SD for continuous variables and n (column %) for categorical variables. ASA, American Society of Anesthesiologists; mYPAS, modified Yale Preoperative Anxiety Scale; OSA, obstructive sleep apnea. High preoperative anxiety was defined a priori as mYPAS score ≥40. *P* values are from Welch t-test, χ^2 test, or Fisher exact test as appropriate, with the corresponding test statistic reported in parentheses when estimable. Percentages may not sum to 100 due to rounding.

We examined mediation by early pain using a regression-based statistical mediation framework, treating esketamine exposure as the exposure, peak FLACC score as the mediator, and emergence agitation as the primary outcome [15]. The mediator model regressed peak FLACC score on esketamine exposure and Model IV covariates using linear regression. The outcome model regressed emergence agitation on esketamine exposure, peak FLACC score, and the same covariates using logistic regression. We estimated direct, indirect, and total association estimates on the odds-ratio scale using non-parametric bootstrap with 5,000 resamples. The proportion mediated was calculated on the log(OR) scale as log(OR_NIE)/log(OR_TE), with percentile 95% CIs derived from the bootstrap distribution.

Sensitivity analyses were prespecified to assess robustness: (1) Redefining emergence agitation as PAED score ≥12; (2) Using Watcha score ≥3 as an alternative agitation definition; (3) Repeating the primary analysis after excluding records with major protocol-documentation deviations; (4) Additionally adjusting the primary model for peak FLACC score to evaluate attenuation; (5) Repeating mediation analysis using moderate-to-severe pain as a binary mediator; (6) Repeating primary analyses using multiple imputation by chained equations with 20 datasets and pooling estimates using Rubin's rules; and (7) Calculating an exploratory E-value for the primary association to describe the minimum strength of unmeasured confounding required to fully explain the observed association. All tests were two-sided with statistical significance defined as P<0.05, and analyses were performed in R (version 4.3.2).

Results

Baseline characteristics

Baseline demographic and perioperative characteristics were broadly comparable between groups (**Table 1**). There were no differences between exposure groups in terms of age, sex, OSA-related symptoms, preoperative anxiety,

adenoid hypertrophy grade, surgery duration, anesthesia duration, mean end-tidal sevoflurane concentration, and intraoperative remifentanil dose (all P>0.05).

Associations of esketamine with emergence agitation, pain, and recovery endpoints

Emergence agitation occurred in 41/120 children (34.2%) in the non-esketamine group and 22/120 (18.3%) in the esketamine group. In the fully adjusted model (Model IV), esketamine use was associated with lower odds of emergence agitation (OR = 0.46, 95% CI 0.25-0.83) and lower peak PAED score (MD = -1.88, 95% CI -2.96 to -0.80). The odds of severe emergence agitation were also lower in the esketamine group (OR = 0.40, 95% CI 0.19-0.86). Early pain showed a parallel pattern, with lower peak FLACC score (MD = -1.15, 95% CI -1.68 to -0.62), lower odds of moderate-to-severe pain (OR = 0.49, 95% CI 0.28-0.86), and lower odds of rescue analgesia (OR = 0.48, 95% CI 0.24-0.95). Across sequential models, estimates changed minimally after covariate adjustment, supporting stability of the primary findings (**Table 2**).

Mediation by early postoperative pain

The mediation analysis supported early pain as a meaningful statistical pathway linking esketamine use to lower emergence agitation. In the mediator model, esketamine exposure was associated with lower peak FLACC score (MD = -1.15, 95% CI -1.68 to -0.62). In the outcome model including both esketamine and peak FLACC score, each 1-point higher peak FLACC score was associated with higher odds of emergence agitation (OR = 1.43, 95% CI 1.23-1.67). The total association estimate for esketamine and emergence agitation was OR_TE = 0.46 (95% CI 0.25-0.83). The indirect pathway through peak FLACC score was statistically significant (OR_NIE = 0.81, 95% CI 0.72-0.92), corresponding to a mediation proportion of 27.2% (95% CI 12.0%-47.0%) on the log(OR) scale. The remaining association, not operating through measured early pain, was represented by the direct pathway estimate (OR_NDE = 0.57, 95% CI 0.32-0.99), consistent with partial statistical mediation (**Table 3** and **Figure 2**).

Subgroup analyses

Subgroup analyses are presented in **Table 4**. The inverse association between esketamine use and emergence agitation was directionally consistent across sex, age group, OSA-related symptoms, adenoid hypertrophy grade, and anesthesia duration strata. We observed a statistically significant interaction for preoperative anxiety (interaction $\chi^2 = 4.18$; P for interaction = 0.041). The association appeared stronger among children with high preoperative anxiety (OR = 0.34, 95% CI 0.16-0.74) than among those without (OR = 0.59, 95% CI 0.22-1.59). A stronger point estimate was also observed among children with anesthesia duration ≥45 minutes (OR = 0.27, 95% CI 0.10-0.71) than among those with shorter duration (OR = 0.64, 95% CI 0.28-1.45), although the interaction did not reach statistical significance (interaction $\chi^2 = 3.28$; P for interaction = 0.070). The adenoid hypertrophy-grade interaction was not significant (interaction $\chi^2 = 0.27$; P for interaction = 0.60). We interpret these subgroup results as exploratory and not as a basis for definitive stratified treatment recommendations.

Safety, longer-term follow-up, and sensitivity analyses

Safety and early recovery profiles are shown in **Table 5**. Esketamine use was associated with a modest, non-significant increase in time to eye opening (9.6±3.2 vs. 8.9±3.0 minutes; P = 0.070, t = 1.82). Extubation time and PACU length of stay did not differ significantly between groups. Rescue analgesia (12.5% vs. 24.2%; P = 0.019, $\chi^2 = 5.51$) and rescue propofol for agitation (8.3% vs. 17.5%; P = 0.034, $\chi^2 = 4.51$) were less common in the esketamine group. Maximum heart-rate and MAP increases from baseline were similar between groups. Respiratory adverse events were uncommon, and no child required unplanned intensive care admission. The incidence of PONV, transient oxygen desaturation, laryngospasm, tachycardia, hypertension, and hallucination or nightmare was low and comparable between groups.

As summarized in **Table 6**, routine Day-7 and Day-30 follow-up data were available for most children and showed no statistically significant between-group differences in caregiver-reported negative postoperative behavior, sleep disturbance, delayed nausea or vomiting, hallucination/nightmare, or unplanned medical visits. These Day-7 and Day-30 comparisons were exploratory and based on subjective caregiver reports. Because standardized behavior or

Table 2. Associations of documented esketamine use with emergence agitation, pain, and early recovery endpoints

Outcome (effect measure)	Model I	Model II	Model III	Model IV (primary)
Emergence agitation, OR (95% CI)	0.43 (0.24 to 0.77)	0.44 (0.25 to 0.79)	0.45 (0.25 to 0.81)	0.46 (0.25 to 0.83); z = -2.54; P = 0.011
Peak PAED score, MD (95% CI)	-2.10 (-3.21 to -0.99)	-2.07 (-3.17 to -0.97)	-1.97 (-3.07 to -0.88)	-1.88 (-2.96 to -0.80); t = -3.41; P<0.001
Severe emergence agitation, OR (95% CI)	0.37 (0.18 to 0.76)	0.38 (0.18 to 0.79)	0.39 (0.18 to 0.82)	0.40 (0.19 to 0.86); z = -2.38; P = 0.017
Peak FLACC score, MD (95% CI)	-1.20 (-1.73 to -0.67)	-1.19 (-1.72 to -0.66)	-1.17 (-1.70 to -0.64)	-1.15 (-1.68 to -0.62); t = -4.25; P<0.001
Moderate-to-severe pain, OR (95% CI)	0.46 (0.27 to 0.78)	0.47 (0.28 to 0.80)	0.48 (0.28 to 0.83)	0.49 (0.28 to 0.86); z = -2.49; P = 0.013
Rescue analgesia, OR (95% CI)	0.45 (0.23 to 0.88)	0.46 (0.24 to 0.90)	0.47 (0.24 to 0.93)	0.48 (0.24 to 0.95); z = -2.09; P = 0.037
Rescue propofol for agitation, OR (95% CI)	0.43 (0.19 to 0.95)	0.43 (0.19 to 0.97)	0.44 (0.20 to 0.99)	0.45 (0.20 to 1.02); z = -1.92; P = 0.055
Time to eye opening, MD min (95% CI)	+0.70 (-0.05 to 1.45)	+0.72 (-0.04 to 1.48)	+0.69 (-0.07 to 1.45)	+0.66 (-0.09 to 1.41); t = 1.72; P = 0.087
PACU length of stay, MD min (95% CI)	+1.60 (-0.78 to 3.98)	+1.54 (-0.84 to 3.92)	+1.48 (-0.90 to 3.86)	+1.43 (-0.96 to 3.82); t = 1.17; P = 0.24

All association estimates compare the esketamine group with the non-esketamine group. Emergence agitation was defined as PAED score ≥10 during the first 30 minutes after PACU arrival. Severe emergence agitation was defined as PAED score ≥12. Moderate-to-severe pain was defined as FLACC score ≥4. ORs <1 indicate lower odds in the esketamine group. Negative mean differences indicate lower scores in the esketamine group. Model IV cells additionally report the Wald z statistic for logistic models or the robust t statistic for linear models, together with the corresponding *P* value. Model I included documented esketamine exposure only. Model II additionally adjusted for age, sex, and body weight. Model III additionally adjusted for American Society of Anesthesiologists (ASA) physical status, OSA-related symptoms, and preoperative modified Yale Preoperative Anxiety Scale (mYPAS) score. Model IV additionally adjusted for surgery duration, anesthesia duration, mean end-tidal sevoflurane concentration, and intraoperative remifentanil dose. ASA, American Society of Anesthesiologists; CI, confidence interval; FLACC, Face, Legs, Activity, Cry, Consolability; MD, mean difference; mYPAS, modified Yale Preoperative Anxiety Scale; OR, odds ratio; OSA, obstructive sleep apnea; PACU, post-anesthesia care unit; PAED, Pediatric Anesthesia Emergence Delirium.

Table 3. Statistical mediation analysis for early postoperative pain as a mediator of the association between documented esketamine use and emergence agitation

Mediation component	Estimate	95% CI	Interpretation
Exposure to mediator	MD = -1.15 FLACC points; t = -4.25; P<0.001	-1.68 to -0.62	Esketamine exposure was associated with lower early pain
Mediator to outcome	OR = 1.43 per 1-point FLACC increase; z = 4.58; P<0.001	1.23 to 1.67	Higher early pain was associated with higher odds of emergence agitation
Total association estimate (OR_TE)	0.46; z = -2.54; P = 0.011	0.25 to 0.83	Overall association between esketamine exposure and emergence agitation
Direct pathway estimate (OR_NDE)	0.57; z = -1.95; P = 0.051	0.32 to 0.99	Association not operating through measured early pain
Indirect pathway estimate (OR_NIE)	0.81; z = -3.37; P<0.001	0.72 to 0.92	Pathway operating through peak FLACC score
Proportion mediated	27.2%; z = 3.05; P = 0.002	12.0% to 47.0%	Calculated on the log(OR) scale

Mediation analysis treated documented esketamine exposure as the exposure, peak FLACC score during the first 30 minutes after PACU arrival as the mediator, and emergence agitation defined as PAED score ≥10 in the PACU as the outcome. Models adjusted for the full Model IV covariate set. Direct pathway, indirect pathway, and total association estimates were estimated using 5,000 non-parametric bootstrap resamples. Test statistics are reported as robust t values for linear mediator models and Wald z values for logistic pathway models, each with the corresponding two-sided *P* value. NDE, natural direct effect; NIE, natural indirect effect; TE, total effect. CI, confidence interval; FLACC, Face, Legs, Activity, Cry, Consolability; MD, mean difference; OR, odds ratio; PACU, post-anesthesia care unit; PAED, Pediatric Anesthesia Emergence Delirium.

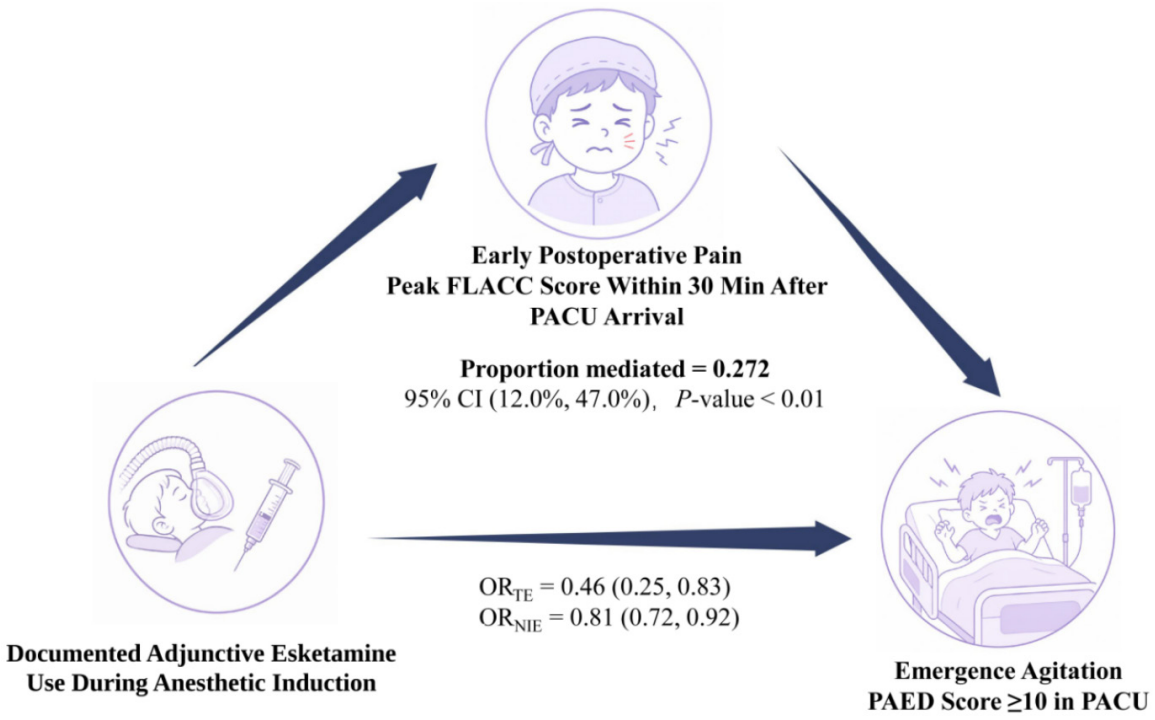

Figure 2. Mediation pathway of early postoperative pain linking documented esketamine use during anesthetic induction to emergence agitation in children undergoing adenoidectomy. The diagram illustrates documented esketamine exposure as the exposure, peak FLACC score during the first 30 minutes after PACU arrival as the mediator, and emergence agitation defined as PAED score ≥10 in the PACU as the outcome. The total association estimate for esketamine exposure and emergence agitation (OR_TE = 0.46, 95% CI 0.25 to 0.83) was partitioned into an indirect pathway estimate through peak FLACC score (OR_NIE = 0.81, 95% CI 0.72 to 0.92; proportion mediated = 27.2%, 95% CI 12.0% to 47.0%) and a direct pathway estimate not operating through measured early pain (OR_NDE = 0.57, 95% CI 0.32 to 0.99).

sleep scale scores, post-30-day agitation-recurrence data, and chronic pain outcomes were absent from the source records, we could not perform quantitative or inferential analysis of these endpoints. The non-significant differences in the recorded items should not be interpreted as evidence of equivalent long-term recovery.

Prespecified sensitivity analyses did not materially change the primary interpretation (**Table 7**). When we used severe emergence agitation as the endpoint, esketamine remained associated with lower odds (OR = 0.40, 95% CI 0.19-0.86). Using Watcha score ≥3 as an alternative endpoint yielded a similar result (OR = 0.47, 95% CI 0.27-0.81). After excluding eight records with major documentation deviations, the association estimate was nearly unchanged (OR = 0.45, 95% CI 0.24-0.84). Additional adjustment for peak FLACC score attenuated the esketamine-emergence agitation association (OR = 0.60, 95% CI 0.32-1.12), consistent with partial pain-related attenuation. The binary-mediator sensitivity analysis also supported an indirect pathway through moderate-to-severe pain (OR_NIE = 0.86, 95% CI 0.77-0.96). Multiple imputation produced a pooled estimate closely aligned with complete-case findings (OR = 0.47, 95% CI 0.26-0.84). The exploratory E-value for the primary OR was 3.77, and the E-value for the upper confidence limit closest to the null was 1.68, suggesting that unmeasured confounding would need to be moderately associated with both exposure and outcome to fully explain the primary association.

Discussion

In this retrospective cross-sectional study of children undergoing adenoidectomy, documented esketamine use during induction was associated with a clinically coherent pattern of more favorable early recovery outcomes, including

Table 4. Subgroup analyses of documented esketamine use and emergence agitation

Subgroup	Category	Non-esketamine group, events/n (%)	Esketamine group, events/n (%)	Adjusted OR (95% CI)	P for interaction (χ^2)
Sex	Female	14/43 (32.6)	7/42 (16.7)	0.42 (0.15 to 1.17)	0.91 (0.01)
	Male	27/77 (35.1)	15/78 (19.2)	0.44 (0.21 to 0.91)	
Age group	3 to 5 years	26/67 (38.8)	13/65 (20.0)	0.38 (0.17 to 0.84)	0.48 (0.50)
	6 to 9 years	15/53 (28.3)	9/55 (16.4)	0.54 (0.21 to 1.37)	
Preoperative anxiety	mYPAS ≥40	28/70 (40.0)	13/68 (19.1)	0.34 (0.16 to 0.74)	0.041 (4.18)
	mYPAS <40	13/50 (26.0)	9/52 (17.3)	0.59 (0.22 to 1.59)	
OSA-related symptoms	Yes	24/58 (41.4)	10/55 (18.2)	0.31 (0.13 to 0.73)	0.19 (1.71)
	No	17/62 (27.4)	12/65 (18.5)	0.60 (0.25 to 1.43)	
Anesthesia duration	<45 min	20/65 (30.8)	14/63 (22.2)	0.64 (0.28 to 1.45)	0.070 (3.28)
	≥45 min	21/55 (38.2)	8/57 (14.0)	0.27 (0.10 to 0.71)	
Adenoid hypertrophy grade	II/III	24/77 (31.2)	14/77 (18.2)	0.47 (0.21 to 1.04)	0.60 (0.27)
	IV	17/43 (39.5)	8/43 (18.6)	0.32 (0.12 to 0.89)	

Adjusted ORs compare the esketamine group with the non-esketamine group within each subgroup and are estimated from Model IV within strata while excluding the stratifying variable where applicable. *P* values for interaction were obtained by adding esketamine-by-subgroup interaction terms to Model IV; the corresponding one-degree-of-freedom interaction chi-square statistic is shown in parentheses. Emergence agitation was defined as PAED score ≥10 during the first 30 minutes after PACU arrival. Severe obstructive sleep apnea requiring planned postoperative intensive monitoring was excluded by design; therefore, the OSA subgroup reflects caregiver-reported OSA-related symptoms rather than severe polysomnography-confirmed disease. CI, confidence interval; FLACC, Face, Legs, Activity, Cry, Consolability; mYPAS, modified Yale Preoperative Anxiety Scale; OR, odds ratio; OSA, obstructive sleep apnea; PACU, post-anesthesia care unit; PAED, Pediatric Anesthesia Emergence Delirium.

Table 5. Recovery characteristics and adverse events by documented esketamine exposure

Outcome	Non-esketamine group (n = 120)	Esketamine group (n = 120)	Association estimate	*P* value
Time to eye opening, min	8.9±3.0	9.6±3.2	MD+0.70	0.070 (t = 1.82)
Extubation time, min	10.5±3.1	11.1±3.4	MD+0.60	0.15 (t = 1.43)
PACU length of stay, min	39.6±9.2	41.2±9.5	MD+1.60	0.18 (t = 1.33)
Rescue analgesia	29 (24.2)	15 (12.5)	OR 0.45	0.019 (χ^2 = 5.51)
Rescue propofol for agitation	21 (17.5)	10 (8.3)	OR 0.43	0.034 (χ^2 = 4.51)
Postoperative nausea or vomiting	9 (7.5)	10 (8.3)	OR 1.12	0.81 (χ^2 = 0.06)
Transient SpO2 <94%	4 (3.3)	3 (2.5)	OR 0.74	>0.99 (Fisher exact)
Laryngospasm	1 (0.8)	2 (1.7)	OR 2.02	>0.99 (Fisher exact)
Tachycardia requiring clinical management	2 (1.7)	4 (3.3)	OR 2.03	0.68 (Fisher exact)
Hypertension requiring clinical management	1 (0.8)	3 (2.5)	OR 3.05	0.62 (Fisher exact)
Hallucination or nightmare before discharge	0 (0.0)	2 (1.7)	Not estimated	0.50 (Fisher exact)
Maximum heart-rate increase from baseline, beats/min	18.6±8.9	19.7±9.1	MD+1.10	0.34 (t = 0.95)
Maximum MAP increase from baseline, mmHg	8.1±5.5	8.8±5.7	MD+0.70	0.33 (t = 0.97)

Values are mean ± SD or n (column %). Association estimates are unadjusted mean differences or odds ratios comparing the esketamine group with the non-esketamine group. *P* values are accompanied by Welch t, χ^2, or Fisher exact test labels as appropriate. Fisher exact test was used for rare safety events and does not yield a single chi-square statistic. MAP, mean arterial pressure; MD, mean difference; OR, odds ratio; PACU, post-anesthesia care unit; PONV, postoperative nausea or vomiting; SD, standard deviation; SpO2, peripheral oxygen saturation.

lower odds of emergence agitation, lower peak PAED and FLACC scores, fewer moderate-to-severe pain events, and reduced need for rescue analgesia. Mediation analysis suggested that early pain accounted for approximately one quarter of the total anti-agitation association. Exploratory follow-up analyses at 1 week and 1 month did not show a statistically significant signal for delayed negative behavior, sleep disturbance, hallucination/nightmare, PONV, or unplanned medical visits. These findings should be interpreted as association and statistical pathway evidence from routine records, not as proof of causal clinical efficacy.

Our findings align with prior evidence that esketamine-based strategies reduce early recovery agitation in children undergoing airway surgery, consistent with two recent meta-analyses of randomized trials reporting that perioperative esketamine lowers emergence delirium incidence and pain scores without prolonging

Table 6. Longer-term postoperative behavior, sleep, and delayed safety outcomes by documented esketamine exposure

Outcome	Non-esketamine group	Esketamine group	Association estimate	*P* value (test statistic)
Day-7 follow-up available	114/120 (95.0)	115/120 (95.8)	OR 1.19	0.78 (chi-square = 0.08)
Day-7 negative postoperative behavior	23/114 (20.2)	14/115 (12.2)	OR 0.55	0.10 (chi-square = 2.72)
Day-7 sleep disturbance	18/114 (15.8)	12/115 (10.4)	OR 0.62	0.22 (chi-square = 1.48)
Day-7 delayed nausea or vomiting	8/114 (7.0)	9/115 (7.8)	OR 1.13	0.81 (chi-square = 0.06)
Day-7 hallucination or nightmare after discharge	1/114 (0.9)	2/115 (1.7)	OR 2.00	>0.99 (Fisher exact)
Day-30 follow-up available	108/120 (90.0)	111/120 (92.5)	OR 1.37	0.50 (chi-square = 0.46)
Day-30 negative postoperative behavior	8/108 (7.4)	6/111 (5.4)	OR 0.71	0.54 (chi-square = 0.37)
Day-30 sleep disturbance	7/108 (6.5)	5/111 (4.5)	OR 0.68	0.52 (chi-square = 0.42)
Day-30 unplanned medical visit	3/108 (2.8)	2/111 (1.8)	OR 0.64	0.68 (Fisher exact)
Day-30 persistent hallucination or nightmare	0/108 (0.0)	0/111 (0.0)	Not estimated	>0.99 (Fisher exact)

Values are n/N (%) unless otherwise indicated. Follow-up outcomes were abstracted from routine postoperative telephone or outpatient records when available and were analyzed as exploratory safety and recovery outcomes. Negative postoperative behavior and sleep disturbance were caregiver-reported new or worsened symptoms compared with the preoperative baseline. *P* values are accompanied by chi-square, Welch t, or Fisher exact labels as appropriate. Validated quantitative behavior and sleep scale scores, recurrent agitation beyond 1 month, and chronic pain outcomes were not collected and therefore are not included in this table. CI, confidence interval; OR, odds ratio.

recovery [16, 17]. This study adds novel evidence by focusing on adenoidectomy without tonsillectomy, examining routine induction-phase esketamine use, and statistically partitioning the anti-agitation association into pain-related and residual components.

The mediation findings are biologically plausible and clinically informative, though interpretably observational. Adenoidectomy may cause early throat discomfort, swallowing pain, airway irritation, and suffocation sensations during recovery, manifesting as crying, restlessness, and inconsolability. Experimental and pharmacologic literature supports that NMDA-receptor activity contributes to central sensitization, and ketamine-class drugs exert analgesia via NMDA antagonism and related network effects [18]. However, this study lacked translational data (e.g., cell/animal experiments, receptor assays, inflammatory biomarkers, electroencephalographic arousal measures), so the observed mediation through FLACC score is only a statistical pathway compatible with pain reduction, not direct evidence that esketamine reduces emergence agitation by downregulating NMDA-receptor-mediated molecular pathways. The partial mediation proportion also implies residual pathways - such as smoother anesthetic transition, reduced environmental reactivity, arousal modulation, reduced opioid-related hyperalgesia, or non-pain sedative/dissociative properties - which may contribute to the anti-agitation effect.

Subgroup findings suggested the inverse association between esketamine use and emergence agitation may be more pronounced in children with high preoperative anxiety, with no statistically significant interaction by adenoid hypertrophy grade or OSA-related symptoms. This is clinically coherent, as anxious children may awaken with greater sympathetic arousal, poorer tolerance of the unfamiliar PACU environment, and stronger behavioral expression of discomfort. Nevertheless, the study was not powered for definitive interaction testing, so the significant anxiety interaction should be regarded as a hypothesis-generating signal rather than a validated basis for individualized treatment allocation. Additionally, the exclusion of severe OSA patients requiring planned intensive monitoring limits our ability to design pre-treatment strategies for the highest-risk sleep-disordered breathing population.

From a clinical translation perspective, we clarify an operational recovery pathway rather than proposing a universally generalizable protocol. This pathway integrates preoperative anxiety stratification, exclusion of severe OSA requiring planned admission, standardized induction and multimodal analgesia, paired PAED/FLACC assessments in the PACU, pain-first rescue for elevated FLACC scores, and escalation to propofol only for agitation that endangers safety or care delivery. This framework may facilitate clinical teaching and prospective multicenter validation is required before it can be adopted as a standardized pediatric adenoidectomy anesthesia pathway.

Several limitations of this work must be acknowledged. First, this was a single-center

Table 7. Prespecified sensitivity analyses for the association between documented esketamine use and emergence agitation

Sensitivity analysis	Sample	Endpoint or model	OR or statistic (95% CI; Wald z; *P* value)	Interpretation
Primary Model IV	n = 240	PAED ≥10	0.46 (0.25 to 0.83); z = -2.54; P = 0.011	Reference association estimate
Severe agitation definition	n = 240	PAED ≥12	0.40 (0.19 to 0.86); z = -2.38; P = 0.017	Consistent direction
Alternative agitation scale	n = 240	Watcha score ≥3	0.47 (0.27 to 0.81); z = -2.69; P = 0.007	Consistent direction
Complete-protocol-documentation analysis	n = 232	PAED ≥10	0.45 (0.24 to 0.84); z = -2.50; P = 0.012	Documentation deviations did not alter findings
Additional adjustment for pain	n = 240	Model IV plus peak FLACC	0.60 (0.32 to 1.12); z = -1.60; P = 0.11	Attenuation consistent with partial mediation
Binary mediator sensitivity	n = 240	Moderate-to-severe pain mediator	OR_NIE 0.86 (0.77 to 0.96); z = -2.68; P = 0.007	Indirect pathway remained present
Multiple imputation	n = 240	Pooled Model IV	0.47 (0.26 to 0.84); z = -2.52; P = 0.012	Aligned with complete-case result
Exploratory E-value analysis	n = 240	Model IV primary endpoint	E-value 3.77; CI-limit 1.68	Quantifies potential unmeasured confounding needed to explain the primary estimate

All odds ratios compare the esketamine group with the non-esketamine group. Primary and sensitivity models used the same Model IV covariate set where applicable. Wald z values and the corresponding two-sided *P* values are reported in the estimate column when available. PAED, Pediatric Anesthesia Emergence Delirium scale; FLACC, Face, Legs, Activity, Cry, Consolability scale; CI, confidence interval; NIE, natural indirect effect; OR, odds ratio; PACU, post-anesthesia care unit.

retrospective cross-sectional study. Exposure was documented during routine care rather than assigned prospectively, so exposure misclassification, selection bias, and residual confounding remain possible despite record cross-checking and multivariable adjustment. Second, statistical mediation cannot establish a molecular mechanism, as no cell, animal, biomarker, or receptor-level experiments were performed. Third, only one induction dose of esketamine (0.3 mg/kg) was observed, leaving dose-response relationships, lower-dose alternatives, higher-dose safety, and optimal timing undetermined; prior pediatric ketamine evidence supports the need for prospective dose-finding work [19], and no age- or anxiety-specific dosing recommendations can be drawn from this single exposure. Consistent with this limitation, future randomized dose-ranging trials should compare several subanesthetic doses and administration times, and evaluate agitation, analgesia, recovery time, and adverse events collectively before an optimal regimen is recommended. Fourth, severe OSA requiring planned postoperative intensive monitoring was excluded, limiting the study's applicability to this high-risk subgroup. Fifth, longer-term follow-up data were abstracted from routine records rather than collected via prospectively administered validated instruments, and incomplete follow-up may have introduced attrition bias; nonstandardized caregiver follow-up and the absence of systematic assessment for recurrent agitation and chronic pain at or beyond 1 month leave these long-term outcomes unknown. Sixth, PAED and FLACC behaviors overlap, and recent evidence emphasizes that observational scales may struggle to distinguish emergence delirium from pain in children who are not fully awake [20-22]. Finally, subgroup interaction analyses and rare adverse-event comparisons were underpowered and should not be overinterpreted unless confirmed in larger multicenter studies [23-25].

In conclusion, documented esketamine use during induction was associated with more favorable early recovery outcomes, including lower odds of emergence agitation, lower peak PAED and FLACC scores, and fewer rescue analgesia requirements, without clinically meaningful prolongation of extubation or PACU stay. Mediation analysis suggested partial statistical mediation through early pain, indicating that differences in early pain intensity may account for a measurable portion of the observed anti-agitation association, alongside additional unmeasured pathways. Exploratory caregiver-reported follow-up revealed no intergroup differences in documented outcomes, but long-term equivalence cannot be concluded due to the lack of validated scales and systematic assessment of agitation recurrence and chronic pain at or beyond 1 month. These findings represent non-causal clinical associations and statistical mediation results; they neither verify an NMDA-receptor mechanism nor identify age- or anxiety-specific dose or timing regimens. Prospective multicenter dose-ranging trials, incorporating mechanistic substudies and validated longitudinal pediatric instruments, are required to address these gaps.

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Disclosure of conflict of interest

None.

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