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CLINICAL TRIAL REPORT

The Effects of Different Doses of Nalbuphine and Esketamine on Prevention of Emergence Agitation in Preschool Children Undergoing Tonsillectomy and Adenoidectomy: A Randomized Clinical Trial

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Purpose: Emergence agitation (EA) is a frequent complication in preschool children following adenotonsillectomy. This study evaluated the efficacy of intravenous nalbuphine versus esketamine for EA prophylaxis in this population.

Patients and Methods: In this randomized, double-blind trial, 98 children (aged 3–7 years) undergoing adenotonsillectomy were analysed via a modified intention-to-treat approach. Patients received esketamine 0.25 mg/kg (Group E, n=33), nalbuphine 0.1 mg/kg (Group N1, n=33), or nalbuphine 0.2 mg/kg (Group N2, n=32) approximately 10 minutes before surgery completion. The primary outcome was EA incidence (maximum Pediatric Anesthesia Emergence Delirium [PAED] score ≥12 within 30 minutes post-extubation). Secondary outcomes included exploratory longitudinal Face, Legs, Activity, Cry, and Consolability (FLACC) scores, haemodynamics, and adverse events.

Results: EA incidence was significantly lower in Group N2 (6.25%) than Group E (39.39%) (Relative Risk [RR] = 0.16; 95% CI: 0.04–0.65; Bonferroni-adjusted $P = 0.006$). The difference between Group N1 (21.21%) and Group E was not statistically significant (RR = 0.54; 95% CI: 0.25–1.18; $P = 0.354$). Exploratory repeated-measures analyses showed Group N2 provided superior analgesia and more stable heart rates postoperatively compared to Group E ($P = 0.004$ for FLACC; $P = 0.002$ for heart rate). Extubation times and adverse event rates were comparable across groups ($P = 0.482$ and $P > 0.999$, respectively).

Conclusion: Prophylactic nalbuphine (0.2 mg/kg) significantly reduces EA incidence in preschool children undergoing adenotonsillectomy compared with esketamine. Exploratory findings suggest it provides stable analgesia and haemodynamics without delaying recovery. These results may inform paediatric anaesthesia guidelines, warranting further multicentre validation.

Keywords: adenotonsillectomy, emergence agitation, esketamine, nalbuphine

Introduction

Emergence agitation (EA) is a distressing clinical phenomenon characterised by dissociation, inconsolability, and motor restlessness during the early recovery phase following general anaesthesia. It is particularly prevalent in preschool-aged children undergoing adenotonsillectomy, with reported incidences of up to 80%.[1] Beyond the immediate peri-operative period, EA is associated with significant safety concerns, including self-injury, surgical site haemorrhage, and inadvertent dislodgement of intravenous catheters, and imposes a substantial psychological and physical burden on caregivers and healthcare staff.[2,3]

The aetiology of EA is multifactorial, involving pharmacological factors (such as the use of rapid-acting volatile anaesthetics), the intensity of surgical stimulation, and baseline psychological vulnerability in children.[4,5] Current preventive strategies commonly rely on pharmacological interventions, including dexmedetomidine and conventional opioids; however,

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their clinical utility is often constrained by concerns regarding dose-dependent bradycardia or opioid-induced respiratory depression, which are particularly relevant in paediatric airway surgery.[6]

Esketamine, the S(+) enantiomer of ketamine, has attracted increasing interest due to its potent N-methyl-D-aspartate (NMDA) receptor antagonism, providing effective analgesia with minimal respiratory suppression.[7,8] Low-dose esketamine has demonstrated excellent efficacy and safety in providing analgesia and reducing EA in various paediatric settings.[8–10] However, its optimal dosing regimen in preschool airway surgery remains under active investigation, as its dissociative properties require careful titration to avoid paradoxical psychotomimetic symptoms. In contrast, nalbuphine—a mixed κ-opioid receptor agonist and μ-opioid receptor antagonist—offers a distinct pharmacological profile. Activation of κ-receptors provides analgesia and sedation, while μ-receptor antagonism confers a ceiling effect on respiratory depression, rendering nalbuphine a potentially attractive option for paediatric airway procedures.[11,12]

Despite its theoretical advantages, the optimal dosing of nalbuphine for EA prophylaxis, and its comparative efficacy relative to NMDA receptor modulation with esketamine, remain poorly defined. The present study was therefore designed to address this knowledge gap. We hypothesised that nalbuphine would confer greater, dose-dependent protection against EA than esketamine by achieving effective analgesia while maintaining a stable emergence profile. Accordingly, this trial compares the efficacy of esketamine (0.25 mg kg^{-1}) with two escalating doses of nalbuphine (0.1 and 0.2 mg kg^{-1}), and applies multivariable analyses to assess the independent effects of these interventions after adjustment for relevant baseline clinical variables.

Materials and Methods

Study Design and Ethics

This prospective, randomized, double-blind, controlled clinical trial was conducted at the Renmin Hospital affiliated with Hubei University of Medicine from September 2025 to December 2025. The study protocol was strictly reviewed and approved by the Institutional Review Board (IRB) of the Renmin Hospital affiliated with Hubei University of Medicine (Approval No. SYRMYY-2025-086). The trial was registered [ChiCTR2500108572] and conducted in full accordance with the Declaration of Helsinki. Prior to enrollment, the legal guardians of all participants provided written informed consent after a detailed explanation of the study objectives and potential risks.

Patient Selection and Eligibility

Children aged 3–7 years scheduled for elective adenotonsillectomy under general anaesthesia were screened for eligibility. Inclusion criteria were an American Society of Anesthesiologists (ASA) physical status of I or II and a body mass index (BMI) between 12 and 24 kg m^{-2}.

Exclusion criteria were applied to minimise potential confounding and included known cardiac, pulmonary, or hepatic dysfunction; a history of neurological or psychiatric disorders; hypersensitivity to the study medications or anaesthetic agents; recent upper respiratory tract infection (within 2 weeks); previous airway surgery; and any intra-operative event necessitating deviation from the standardised anaesthetic protocol.

Randomization and Double-Blinding

Eligible participants were randomly allocated in a 1: 1: 1 ratio to receive esketamine (Jiangsu Hengrui Pharmaceuticals Co., Ltd., Jiangsu, China) 0.25 mg kg^{-1} (Group E), nalbuphine (Yangtze River Pharmaceutical Group Jiangsu Zilong Pharm, Jiangsu, China) 0.1 mg kg^{-1} (Group N1), or nalbuphine 0.2 mg kg^{-1} (Group N2). Randomisation was performed using a computer-generated random number sequence.

To strictly maintain double-blinding despite the different drug dosages, an independent pharmacist prepared the study medications. All assigned drugs were diluted with 0.9% sodium chloride to an identical total volume of 10 mL. Consequently, all syringes were completely indistinguishable in physical appearance, colour, and volume, ensuring that the blinding of the administering anaesthesiologists and PACU assessors was not broken.

Standardized Anesthesia Protocol

All patients adhered to standard pre-operative fasting guidelines (8 h for solids and 2 h for clear fluids), and no sedative premedication was administered. Upon arrival in the operating theatre, standard monitoring, including electrocardiography, pulse oximetry, and non-invasive blood pressure measurement, was instituted. General anaesthesia was induced via inhalation of sevoflurane 8% in 100% oxygen at a fresh gas flow of 5 L min^{-1}. After loss of consciousness, an intravenous cannula was inserted, and penehyclidine hydrochloride (0.01 mg kg^{-1}, Chongqing Pharscin Pharmaceutical Co., Ltd., Chongqing, China) was administered to reduce airway secretions. Tracheal intubation was facilitated with intravenous propofol (2–3 mg kg^{-1}, Guangdong Jia Bo Pharmaceutical Co., Ltd., Guangdong, China), cisatracurium (0.15–0.2 mg kg^{-1}, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Jiangsu, China), and remifentanil (2 μg kg^{-1}, Yichang Humanwell Pharmaceuticals Co., Ltd., Yichang, China).

Anaesthesia was maintained with sevoflurane (end-tidal concentration 2–4%) in a 50% oxygen–air mixture, together with a continuous infusion of remifentanil (0.1–0.4 μg kg^{-1} min^{-1}). The remifentanil infusion was titrated to maintain haemodynamic variables within 20% of baseline values. Intra-operative analgesia and prophylaxis against postoperative nausea and vomiting were standardised across all groups with intravenous parecoxib sodium (1 mg kg^{-1}, Sailong Pharmaceutical Group Co,Ltd., Hunan, China) and dexamethasone (0.1 mg kg^{-1}, Tianjin King York Group Hubei Tianyao Pharmaceutical Co., Ltd., Hubei, China).

Pharmacological Intervention

Approximately 10 minutes prior to the estimated completion of surgery, the assigned study medication (esketamine or nalbuphine) was administered intravenously over 60s. At the completion of the procedure, all anaesthetic agents were discontinued. Tracheal extubation was performed in the operating room once standard clinical criteria were met, including adequate spontaneous ventilation and purposeful movement. Subsequently, patients were transferred to the post-anaesthesia care unit (PACU).

Outcome Measures and Definitions

The primary outcome was the incidence of EA during the first 30 min post-extubation, defined as a maximum Pediatric Anesthesia Emergence Delirium (PAED) score ≥12.

Secondary outcomes included:

1) Preoperative agitation: pre-admission PAED score, assessed immediately prior to entry into the operating theatre (T0).
2) Severity of EA: PAED scores recorded during the first 30 min post-extubation and the incidence of severe EA, defined as a PAED score >15.
3) Postoperative pain: assessed using the Face, Legs, Activity, Cry, and Consolability (FLACC) scale (0–10) at four timepoints: immediately post-extubation (T1), and at 10, 20, and 30 min post-extubation (T2–T4).
4) Haemodynamic stability: heart rate (HR) and peripheral oxygen saturation (SpO_2) recorded at T1–T4.
5) Recovery profiles: extubation time (from cessation of anaesthesia to extubation) and total PACU stay.
6) Adverse events: incidence of nausea, vomiting, hypoxaemia (SpO_2 <90%), respiratory depression (rate <10 breaths min^{-1}), and delayed awakening (>60 min).

Statistical Analysis

Sample size was determined based on a pilot study, which reported an EA incidence of 40% in Group E and 10% in Group N2. To achieve 80% power ($\beta = 0.2$) at a two-sided significance level of 0.05 ($\alpha = 0.05$), 30 patients per group were required. Allowing for an anticipated 10% attrition rate, 33 participants were enrolled per group, yielding a total sample size of 99. Efficacy and safety analyses were conducted based on a modified Intention-to-Treat (mITT) analysis set, defined as all randomized participants who received the assigned study medication, completed the surgical procedure, and had evaluable postoperative data for the primary outcome.

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk test and are presented as mean ± standard deviation (SD) or median [interquartile range, IQR] as appropriate. Prior to parametric analyses, the homogeneity of variances was formally evaluated using Levene's test. When the assumption of homoscedasticity was satisfied, continuous data were analyzed using a standard one-way analysis of variance (ANOVA) followed by Bonferroni-adjusted post-hoc tests. If the assumption of variance homogeneity was violated, Welch's ANOVA was utilized, followed by the Games-Howell post-hoc test. Non-normally distributed continuous or ordinal variables (eg., maximum PAED scores, extubation times) were compared using the Kruskal–Wallis test, followed by Dunn's post-hoc test with Bonferroni correction for multiple comparisons.

For the primary endpoint (confirmatory analysis), the incidence of EA was compared among the three groups using the Chi-square test or Fisher's exact test. To explicitly control the family-wise Type I error rate for the primary outcome across the three study arms, pairwise comparisons were adjusted using the Bonferroni method, with statistical significance set at a stricter threshold of $P < 0.0167$ (0.05/3). Treatment effects for the primary outcome are presented as unadjusted Relative Risks (RR) and Absolute Risk Reductions (ARR) with 95% confidence intervals (CIs). To prevent model overfitting given the limited total number of EA events, extensive multivariable adjustment was restricted. Instead, a simplified multivariable logistic regression model—adjusting only for the treatment group and the preoperative PAED score (the most clinically relevant baseline covariate)—was conducted as a sensitivity analysis.

All secondary endpoint analyses were pre-designated as exploratory. Longitudinal continuous outcomes measured repeatedly at the same intervals (FLACC scores, heart rate, and SpO_2 at T1–T4) were analyzed using a Repeated-Measures Analysis of Variance (RM-ANOVA). Mauchly's test was used to assess the assumption of sphericity, and Greenhouse–Geisser corrections were applied where the assumption was violated. In this framework, "Group" was entered as a between-subject factor, "Time" as a within-subject factor, and the "Group × Time" interaction was evaluated to account for within-patient correlation. Throughout the manuscript, exact P values are reported to three decimal places (except where $P < 0.001$), and an adjusted $P < 0.05$ was considered statistically significant for secondary analyses.

Results

Patient Flow and Baseline Characteristics

A total of 99 children were initially screened and randomized. One patient in Group N2 experienced significant postoperative primary hemorrhage necessitating immediate surgical re-intervention. As this adverse event precluded the assessment of EA, the patient was excluded from the efficacy analysis set per the prespecified modified Intention-to-Treat (mITT) principle. Consequently, 98 participants constituted the final mITT population: Group E (n = 33), Group N1 (n = 33), and Group N2 (n = 32). The flow of participants is summarized in the CONSORT diagram (Figure 1).

Baseline demographic variables, including age, sex, and body mass index, were highly comparable across the three groups. Perioperative characteristics, including the duration of surgery and pre-admission PAED scores, did not differ significantly among the groups, confirming optimal baseline comparability (Table 1).

Primary Outcome: Incidence of Emergence Agitation

The overall incidence of EA (prespecified as a maximum PAED score ≥12) within the first 30 min post-extubation demonstrated a dose-dependent reduction in the nalbuphine groups compared with the esketamine group. The incidence of EA was 39.4% (13/33) in Group E, 21.2% (7/33) in Group N1, and 6.3% (2/32) in Group N2 (Overall Chi-square, $P = 0.008$).

To provide clinically interpretable effect estimates and strictly control for multiplicity, unadjusted Relative Risks (RR) with 95% confidence intervals (CI) were calculated alongside Bonferroni-adjusted pairwise comparisons. Group N2 had a significantly lower incidence of EA than Group E (unadjusted RR = 0.16; 95% CI: 0.04 to 0.65; Bonferroni-adjusted $P = 0.006$), corresponding to a robust Absolute Risk Reduction (ARR) of 33.1%. Although the incidence in Group N1 was lower than in Group E, this difference did not reach statistical significance after adjustment for multiple comparisons (unadjusted RR = 0.54; 95% CI: 0.25 to 1.18; Bonferroni-adjusted $P = 0.354$). The incidence of severe EA (PAED score ≥ 15) followed a similar pattern: 15.2% in Group E, 6.1% in Group N1, and 0% in Group N2 (Overall Fisher's exact test $P = 0.038$) (Table 2).

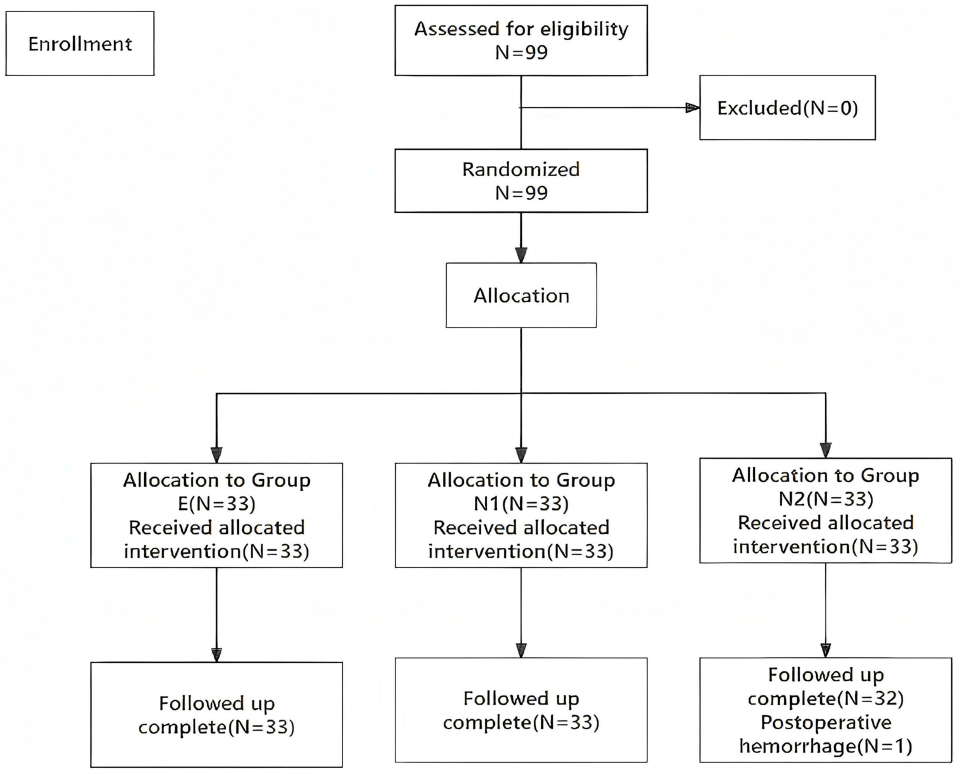

Figure 1 CONSORT Flow diagram of the study.

Sensitivity and Simplified Multivariable Analysis

Given the limited total number of EA events (n = 22), fitting an extensive multivariable logistic regression model with all baseline characteristics risked model overfitting and instability. Therefore, a simplified, parsimonious multivariable

Table 1 Baseline Characteristics Between Three Groups

Characteristics	Group E (n=33)	Group N1 (n=33)	Group N2 (n=32)	*P*-value
Gender (boy)	24 (72.7)	20 (60.6)	21 (65.6)	0.510
Age (years)	5.7±1.1	5.8±1.1	5.9±1.0	0.760
BMI (kg/m^2)	15.7±2.1	15.8±2.3	15.3±2.0	0.588
Operating time (min)	39.7±32.7	30.7±14.4	35.6±21.5	0.453
Pre-admission PAED scores	5.4±2.7	5.0±2.6	5.0±2.8	0.697

Notes: Data are presented as mean ± SD or number (%). *P* values were calculated using One-way ANOVA for continuous normally distributed variables (Age, BMI), the Kruskal–Wallis test for non-normally distributed variables (Operating time, Pre-admission PAED), and the Chi-square test for categorical variables (Gender).

Table 2 The Incidence of EA and PAED Scores Between Three Groups

Characteristics	Group E (n=33)	Group N1 (n=33)	Group N2 (n=32)	*P*-value
EA (PAED≥12), N (%)	13 (39.39)	7 (21.21)	2 (6.25)*	0.008
Severe EA (PAED≥15), N (%)	5 (15.15)	2 (6.06)	0 (0)	0.038
Maximum PAED scores	10.64 ± 4.11	7.76 ± 4.27*	4.88 ± 3.19*$^{\#}$	< 0.001

Notes: Data are presented as mean ± SD or number (%). Overall *P* values were calculated using the Chi-square test (EA incidence), Fisher's exact test (Severe EA), and Kruskal–Wallis test (PAED scores).For the primary outcome (EA incidence), unadjusted pairwise comparisons with Bonferroni correction revealed a significant reduction in Group N2 vs. Group E (Relative Risk [RR] = 0.16; 95% CI: 0.04 to 0.65; adjusted *P* = 0.006). Group N1 vs. Group E did not reach statistical significance after multiplicity adjustment (RR = 0.54; 95% CI: 0.25 to 1.18; adjusted *P* = 0.354).*: adjusted *P*<0.05 compared with group E; $^{\#}$: adjusted *P*<0.05 compared with group N1.

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logistic regression model was constructed as a sensitivity analysis, adjusting only for the treatment group and the most clinically relevant baseline covariate (preoperative PAED score). After adjustment, the administration of nalbuphine 0.2 mg/kg (Group N2) remained an independent and robust protective factor against postoperative EA. In contrast, higher preoperative PAED scores were independently associated with an increased risk of postoperative EA (Figure 2).

Exploratory Secondary Outcomes: PAED, FLACC, and Haemodynamic Stability

Regarding the severity of EA, the single maximum PAED score recorded during the entire 30-minute recovery period was significantly lower in Group N2 compared with the other groups (Kruskal–Wallis $P < 0.001$) (Figure 3A).

For the longitudinal assessment of postoperative pain, a Repeated-Measures ANOVA (RM-ANOVA) of FLACC scores at T1–T4 revealed a significant main effect of group ($F = 5.879$, $P = 0.004$) and time ($F = 21.793$, $P < 0.001$), reflecting a general trend of pain alleviation over time. Importantly, there was no significant group-by-time interaction ($P = 0.646$), indicating that the superior and sustained analgesic advantage provided by 0.2 mg/kg nalbuphine (Group N2) was consistently maintained across all postoperative time points compared to Group E (Figure 3B).

Haemodynamic monitoring further corroborated this stability. RM-ANOVA for heart rate demonstrated a highly significant main effect of group ($F = 6.674$, $P = 0.002$), but no significant main effect of time ($P = 0.695$) or group-by-time interaction ($P = 0.883$). Clinically, this non-significant interaction reveals that the heart rates in the nalbuphine groups remained exceptionally stable, avoiding drastic sympathetic fluctuations throughout the entire 30-minute extubation and recovery phase. Peripheral oxygen saturation (SpO_2) remained highly stable across all groups throughout the recovery period. RM-ANOVA confirmed no significant main effect of group ($P = 0.397$), time ($P = 0.286$), or group-by-time interaction ($P = 0.873$), with no episodes of clinically significant desaturation observed (Table 3).

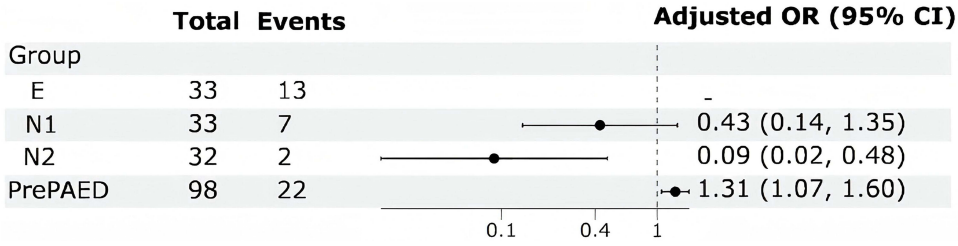

Figure 2 Forest plot of adjusted odds ratios for risk factors of postoperative EA.

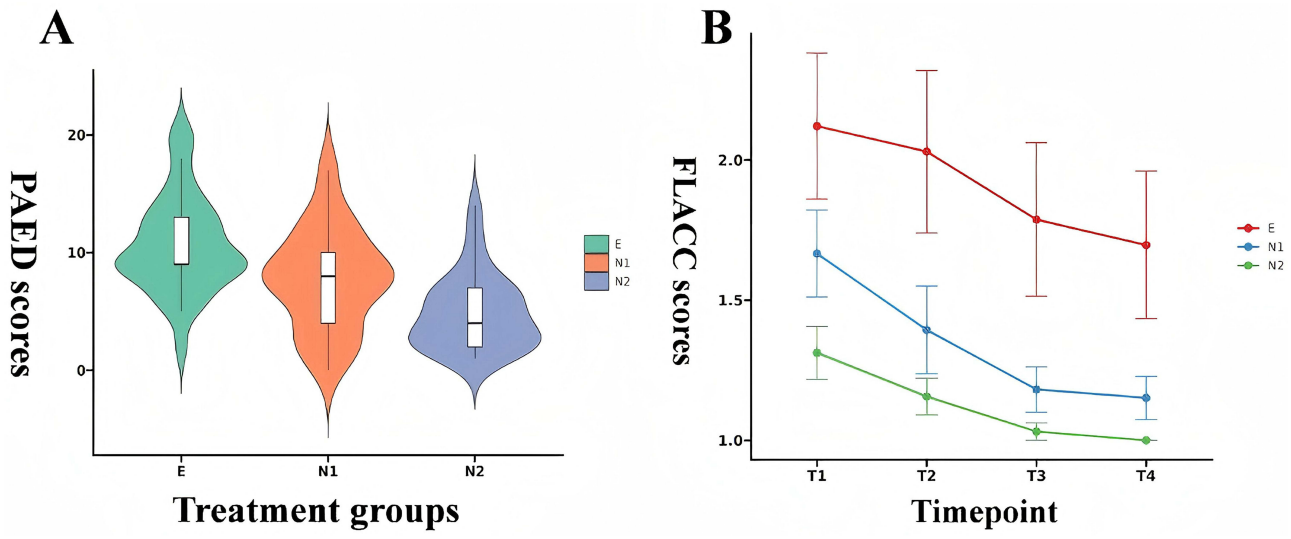

Figure 3 PAED and FLACC scores between three groups. (**A**) Maximum PAED scores during the 30-min recovery phase. (**B**) Longitudinal FLACC scores.

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Table 3 Comparison of HR and SpO_2 between Three Groups After Extubation

Parameter	Timepoint	Group E (n=33)	Group N1 (n=33)	Group N2 (n=32)	P_{Group}	P_{Time}	$P_{Group×Time}$
Heart rate (bpm)	T1	100.0 ± 16.8	94.1 ± 13.6	91.2 ± 9.2*	0.002	0.695	0.883
	T2	100.1 ± 13.9	92.6 ± 11.0*	90.8 ± 7.6*			
	T3	100.8 ± 14.3	92.8 ± 10.5*	92.6 ± 7.6*			
	T4	98.9 ± 15.1	92.1 ± 8.4*	92.0 ± 7.4*			
SpO_2 (%)	T1	98.6 ± 2.0	98.8 ± 1.3	99.1 ± 0.9	0.397	0.286	0.873
	T2	98.7 ± 1.2	98.8 ± 0.9	98.8 ± 0.9			
	T3	98.6 ± 1.3	98.7 ± 1.1	99.0 ± 0.9			
	T4	98.5 ± 1.3	98.6 ± 1.4	98.7 ± 1.3			

Notes: Data are presented as mean ± SD. The exact *P*-values for the main effects of treatment group (P_{Group}), time (P_{Time}), and their interaction ($P_{Group×Time}$) were calculated using a Repeated-Measures Analysis of Variance (RM-ANOVA). *: $P < 0.05$ compared with Group E at the same timepoint, based on Bonferroni-adjusted post-hoc pairwise comparisons.

Table 4 Comparison of Recovery Quality and Adverse Events Between Three Groups

Characteristics	Group E	Group N1	Group N2	P-value
Extubation time (min)	21.1 (16.5, 25)	23.1 (19.5, 25)	25.0 (19.3, 30)	0.482
Length of PACU stay (min)	55.2 (47, 61)	57.6 (54, 60)	59.7 (54, 61.8)	0.371
Nausea/Vomiting	1 (3.03)	0 (0.00)	0 (0.00)	1.000
Hypoxic	1 (3.03)	0 (0.00)	0 (0.00)	1.000
Respiratory depression	2 (6.06)	1 (3.03)	1 (3.13)	1.000
Delayed awakening	0 (0.00)	0 (0.00)	0 (0.00)	1.000
Remedial analgesia	3 (9.09)	1 (3.03)	0 (0.00)	0.103

Notes: Data are presented as median (IQR) or number (%). *P* values were calculated using the Kruskal–Wallis test for recovery times and Fisher's exact test for adverse events.

Recovery Profiles and Safety

Recovery metrics, including time to extubation (Kruskal–Wallis $P = 0.482$) and total post-anaesthesia care unit (PACU) stay (Kruskal–Wallis $P = 0.371$), were highly comparable across the three groups, indicating that neither dose of nalbuphine delayed emergence or PACU discharge (Table 4).

The overall incidence of adverse events was exceptionally low (Group E: 12.1%; Group N1: 6.1%; Group N2: 3.1%) and did not differ significantly between groups. Crucially, no instances of nalbuphine-induced delayed awakening or respiratory depression were observed, affirming the favorable safety profile of prophylactic nalbuphine in paediatric airway procedures.

Discussion

EA remains a common and challenging complication in paediatric anaesthesia, characterised by a paradoxical state of cortical arousal despite reduced conscious awareness. In preschool children undergoing adenotonsillectomy, the combination of sevoflurane's rapid pharmacokinetics and the intense nociceptive stimulus of airway surgery create a high-risk environment for EA. Children who experience EA are at increased risk of postoperative behavioural disturbances that may extend beyond the immediate recovery period.[13] In this study, EA was assessed using the widely validated PAED scale, which has demonstrated a sensitivity of 100% and a specificity of 94.5%,[14] supporting its use in this clinical setting. This randomised trial showed that intravenous nalbuphine 0.2 mg kg^{-1} significantly reduced the incidence and severity of EA compared with esketamine 0.25 mg kg^{-1}, achieving this effect without prolonging recovery or increasing adverse events.

The superior efficacy of nalbuphine 0.2 mg kg^{-1} is likely attributable to its distinctive pharmacodynamic profile. As a κ-opioid receptor agonist and μ-opioid receptor antagonist,[15,16] nalbuphine targets both key components of EA: nociceptive stimuli and psychological distress. Activation of κ-receptors in the spinal cord and brain provides potent visceral analgesia while inducing a state of "quiet sedation",[17] which contrasts with the "dissociative sedation" produced by NMDA receptor antagonists such as esketamine.[18] In the present study, nalbuphine also provided superior postoperative analgesia without prolonging extubation time or PACU stay, and without increasing the incidence of adverse events. With a rapid onset of action

(within 2 min) and peak plasma concentrations approximately 30 min after administration, nalbuphine is well suited for the prevention of EA, which typically occurs within the first 15 min post-emergence.[19] Similarly, the 10-minute pre-extubation administration timing is also optimal for esketamine. Intravenous esketamine possesses a rapid onset, reaching peak central nervous system concentrations within 1 to 2 minutes, with an initial redistribution half-life of 10 to 15 minutes. This timing ensures that its peak pharmacological effects directly overlap with the intense stimulation of airway clearance and extubation.

In the present study, the incidence of EA in the esketamine group reached 39.4%. While esketamine provides excellent analgesia and effectively reduces EA in many paediatric contexts, its dissociative profile necessitates precise dose titration in young children to prevent potential dysphoria.[20,21] By contrast, nalbuphine appeared to stabilise haemodynamics, as reflected by the significantly lower heart rates observed in Group N2, suggesting effective attenuation of the perioperative stress response and sympathetic activation, which are recognised contributors to EA.

A key finding of this study was the dose-dependent protective effect of nalbuphine. Although Group N1 (0.1 mg kg^{-1}) showed a downward trend in EA incidence, it was the 0.2 mg kg^{-1} dose that achieved both statistical and clinical significance. This higher dose provided sustained analgesia, reflected in consistently lower FLACC scores up to 30 min post-extubation. Postoperative pain is a well-recognised contributor to EA, particularly following sevoflurane-based anaesthesia,[22] with previous reports indicating that the risk of EA increases by approximately 30% for each 1-point increase in the FLACC score.[23] Importantly, despite the higher dose, no instances of delayed awakening or respiratory depression were observed. This favourable safety profile is attributable to the "ceiling effect" of nalbuphine on respiratory depression, a consequence of its μ-receptor antagonism.[24] This characteristic makes 0.2 mg kg^{-1} nalbuphine an attractive option for paediatric airway surgery, where the balance between effective opioid analgesia and the risk of post-obstructive respiratory failure is a primary concern.[25,26] Other opioids, such as sufentanil, alfentanil, and fentanyl, have been shown to reduce EA; however, their use is limited by adverse effects including respiratory depression and postoperative nausea or vomiting.[27–30] Similarly, sedatives such as propofol, midazolam, and dexmedetomidine have been investigated for EA prevention but may cause delayed emergence or bradycardia.[31–34] These side effects are particularly concerning in paediatric patients, who have lower oxygen reserves and higher oxygen consumption than adults.

Multivariable logistic regression analysis revealed that preoperative PAED score is an independent risk factor for postoperative EA, indicating that a child's baseline psychological state may influence recovery trajectory. The low adjusted odds ratio (aOR 0.07) for Group N2 suggests that nalbuphine 0.2 mg kg^{-1} is effective in mitigating this risk, providing both analgesic and behavioural stabilisation during emergence from anaesthesia.

From a clinical perspective, our findings support the administration of nalbuphine 0.2 mg kg^{-1} 10 min before the end of surgery as part of a multimodal strategy for EA prophylaxis. This timing aligns peak plasma concentrations with the critical extubation period, promoting smooth emergence.

Several limitations should be acknowledged. First, although the sample size was adequately powered for the primary outcome, this was a single-centre study. Therefore, future large-scale, multicentre randomized trials are warranted to validate these findings across diverse clinical settings. Second, only a single sub-anaesthetic dose of esketamine was evaluated; future studies could investigate alternative dosing regimens or combinations with other sedatives to assess their impact on emergence. Third, the a priori sample size calculation did not inflate the required number of participants to account for multiple pairwise comparisons. Nevertheless, because the observed effect size between Group N2 and Group E was substantial, post-hoc recalculations confirmed that the study maintained adequate power (>80%) even at the strictly penalized Bonferroni threshold. Finally, long-term behavioural follow-up beyond the immediate 24-hour postoperative period would provide a more comprehensive assessment of these interventions.

Conclusion

In conclusion, prophylactic administration of intravenous nalbuphine at 0.2 mg/kg significantly mitigates the incidence of emergence agitation in preschool children undergoing adenotonsillectomy compared with esketamine. Exploratory secondary analyses suggest that this dose may also be associated with stable postoperative analgesia and haemodynamics without prolonging extubation. These primary findings support the use of 0.2 mg/kg nalbuphine as an effective pharmacological strategy for EA prophylaxis in this high-risk population. Furthermore, our results hold potential implications for updating paediatric anaesthesia clinical guidelines regarding optimal EA management.

Abbreviations

ASA, American Society Anesthesiologists; BMI, Body Mass Index; PAED, Pediatric Anesthesia Emergence Delirium; EA, emergence agitation; FLACC, the Face, Legs, Activity, Cry, and Consolability; HR, heart rate; SpO_2, oxygen saturation; PACU, post-anaesthesia care unit.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to institutional restrictions.

Ethics Approval and Informed Consent

The study protocol was strictly reviewed and approved by the Institutional Review Board (IRB) of the Renmin Hospital affiliated with Hubei University of Medicine (Approval No. SYRMYY-2025-086). The trial was registered [ChiCTR2500108572] and conducted in full accordance with the Declaration of Helsinki.Prior to enrollment, the legal guardians of all participants provided written informed consent after a detailed explanation of the study objectives and potential risks.

Consent for Publication

Individual consent was obtained from all participating patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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