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Dose-dependent Immunomodulatory Effects of Esketamine in Pediatric Adenotonsillectomy

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ABSTRACT

Surgical stress in pediatric adenotonsillectomy can trigger marked immune and inflammatory disturbances. Esketamine, beyond its anesthetic role, has been reported to exhibit immunomodulatory and anti-inflammatory properties. However, its dose-dependent impact on perioperative immune homeostasis in children remains unclear. This study aimed to investigate the impact of varying doses of esketamine on perioperative inflammatory cytokines, immune cell balance, and humoral immune markers in pediatric patients undergoing adenotonsillectomy.

Ninety pediatric patients (3–10 years) were retrospectively assigned into three groups based on the esketamine dose they received: low-dose (0.25 mg/kg), medium-dose (0.5 mg/kg), or high-dose (1 mg/kg) esketamine. Serum levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) were measured to assess systemic inflammation, while $CD4^+/CD8^+$ ratios, immunoglobulin (Ig) A, and IgG were evaluated as immune function indices at baseline, 1 hour, and 24 hours postoperatively. Hemodynamic parameters and clinical recovery indices were also recorded.

Compared with the low-dose and high-dose groups, the 0.5 mg/kg esketamine group showed significantly attenuated elevations in IL-6 and CRP, a faster normalization of the $CD4^+/CD8^+$ ratio, and preservation of IgA levels within near-normal range. These immunological benefits coincided with improved postoperative recovery and fewer adverse events. No significant differences were observed in IgG levels among groups.

This study identifies 0.5 mg/kg as a potential immunoprotective threshold for esketamine, effectively mitigating perioperative immune suppression and excessive inflammation in children undergoing adenotonsillectomy, an insight beyond its known anesthetic properties.

Keywords: Adenoidectomy; Child; Esketamine; Immunomodulation; Inflammation; Tonsillectomy

INTRODUCTION

Adenotonsillectomy is one of the most common elective surgeries in pediatric otorhinolaryngology and is mainly used to treat obstructive sleep apnea syndrome (OSAS), recurrent infections, and swallowing dysfunction due to adenoid or tonsil hypertrophy.[1] With the popularization of low-temperature plasma technology, surgical trauma has been significantly reduced, but anesthesia management still faces multiple challenges: narrow airway in children, short surgical time, high incidence of postoperative emergence

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agitation (EA) (up to 40%–60%), and surgical stress may induce systemic inflammatory response and immunosuppression, which may affect the postoperative recovery. Therefore, how to optimize the anesthesia regimen to maintain intraoperative hemodynamic stability, reduce the inflammatory response, and improve the quality of postoperative recovery has become a hot topic in clinical research.

Esketamine has attracted considerable interest in recent years due to its novel mechanism of action as an *N*-methyl-D-aspartate (NMDA) receptor antagonist. This innovative compound exhibits unique neuropharmacological characteristics that distinguish it from conventional agents. Compared with traditional ketamine, esketamine has 2 to 2.5 times higher analgesic efficacy, faster metabolism, and fewer adverse psychiatric effects, which makes it particularly suitable for pediatric anesthesia.[2] Its mechanism of action includes blocking NMDA receptors to reduce the transmission and sensitization of nociception in the central nervous system, thus producing analgesia[3]; during anesthesia, esketamine can regulate the activity of the sympathetic nervous system, which can help to maintain the stability of hemodynamics, and reduce fluctuations in blood pressure and heart rate (HR)[4]; and through the inhibition of the nuclear factor κB (NF-κB) pathway to reduce the proinflammatory factors (eg, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)) release, thereby reducing postoperative inflammatory responses.[5] However, the dose-effect relationship of esketamine has not been fully clarified, especially in pediatric adenotonsillectomy, and the effects of different doses on hemodynamic fluctuations, immune-inflammatory responses, and postoperative recovery remain controversial.

The physiological characteristics of pediatric adenotonsillectomy patients determine the specificity of anesthetic management.[6] First, tonsillar and adenoid hypertrophy may be combined with upper airway obstruction, increasing the difficulty of intubation and postoperative airway risk.[7,8] Secondly, surgical operation stimulates the pharyngeal vagus nerve, which is prone to cause dramatic fluctuations in HR and mean arterial pressure (MAP), while traditional opioids (eg, fentanyl), although able to inhibit the stress response, may cause respiratory depression and postoperative nausea and vomiting (PONV).[9] In addition, the incidence of postoperative awakening agitation (Pediatric Anesthesia Emergence Delirium [PAED] score ≥10) is significantly higher in children than in adults, which is closely related to pain, residual inhalation anesthetic, and inflammatory response and may trigger complications such as trauma bleeding and catheter dislodgement. In recent years, multicenter studies have shown that the anesthesia regimen of sevoflurane combined with remifentanil cannot effectively control postoperative agitation and inflammatory reactions, although it can shorten the awakening time. While benzodiazepines (eg, midazolam) can reduce agitation, they may prolong awakening time and suppress immune function.[10] Therefore, there is an urgent need to explore adjuvant anesthesia drugs that combine analgesic, anti-inflammatory, and hemodynamic stabilizing effects.

The unique advantage of esketamine is its "bidirectional modulation": Low-dose esketamine (0.25–0.5 mg/kg) exhibits a dual ability to provide sedation/analgesia and to maintain hemodynamic stability; this is mediated by sympathetic activation, which thereby sustains cardiac output and blood pressure, while medium to high doses (0.5–1.0 mg/kg) further inhibit the release of inflammatory factors. A 2023 RCT in *Pediatric Anesthesia* reported that pediatric tonsillectomy patients receiving 0.5 mg/kg esketamine exhibited a 35% decrease in postoperative IL-6 levels, alongside a 40% reduction in PAED scores, relative to controls.[11] Another study in elderly patients showed that 0.3 mg/kg esketamine stabilized intraoperative MAP fluctuations but had no significant effect on postoperative delirium (POD), suggesting that there may be an age difference in the dose effect.[12] However, dose selection remains a point of controversy. Some studies have suggested that high doses (1.0 mg/kg) may result in transient hypertension due to excessive sympathetic activation and a dose-related increased risk of nausea and vomiting.[13] In addition, the effects of esketamine on immune function have not been fully elucidated. A 2025 study showed that esketamine attenuated systemic inflammatory responses in thoracic surgery patients, possibly by modulating the phenotypic transformation of monocytes.[14] Animal experiments in 2024 in *Frontiers in Immunology* demonstrated that ketamine can be used to reduce the inflammatory response in patients undergoing thoracic surgery via the Toll-like receptor 4 (TLR4)/NF-κB pathway, but high doses may suppress the $CD4^+/CD8^+$ ratio, suggesting a "double-edged sword" effect in immunomodulation.[15,16]

Although the existing literature has initially explored the use of esketamine in pediatric surgery, most studies focused on a single dose, lacked systematic comparisons of different dose gradients, were mostly limited to intraoperative phases of hemodynamic monitoring, and paid insufficient attention to the dynamic changes during the extubation period and the 24-hour postoperative period, and lacked an analysis of cellular balance of immunoinflammatory indicators and immune cell subsets, leading to high heterogeneity of conclusions. Therefore, the present study proposes the following hypothesis: in pediatric adenotonsillectomy, a moderate dose (0.5 mg/kg) of esketamine significantly improves perioperative hemodynamic stability, more effectively modulates postoperative immune-inflammatory responses, and enhances the quality of postoperative recovery with a better safety profile compared with low (0.25 mg/kg) and high (1 mg/kg) doses. This research was designed to assess the efficacy-safety profile of esketamine across varying doses, facilitating evidence-based anesthesia for pediatric adenotonsillectomy.

MATERIALS AND METHODS

General Information

The study was conducted on 90 children who had received adenotonsillectomy at our center during the 2-year period from June 2021 to June 2023. Through electronic medical record review, based on the administered esketamine dose, participants were stratified into three groups (n=30 each): a low-dose (LD) group (0.25 mg/kg), a medium-dose (MD) group (0.5 mg/kg), and a high-dose (HD) group (1 mg/kg). This study received ethics approval from the Ethics Committee of Baoding Second Central Hospital (approval number: 2023-43). On account of the retrospective study design, the analysis was based on previous clinical archived data, and the ethics committee has approved the exemption of informed consent. All study data were anonymized to ensure the privacy and identity of the participants. Inclusion criteria: children aged 3 to 12 years, weighing 15 to 50 kg, with body mass index (BMI) within the normal range for children of the same age; meeting the indications for adenotonsillectomy (OSAS, recurrent tonsillitis, or hypertrophy of more than III degree); American Society of Anesthesiologists (ASA) classification: I–II, no cardiopulmonary insufficiency, normal liver and renal function (alanine aminotransferase/aspartate aminotransferase <1.5 times upper limit, serum creatinine <80 μmol/L); estimated operative time of 30 to 60 minutes, no history of difficult airway; guardian's consent to participate in the study and cooperation in postoperative follow-up. Exclusion criteria: known allergy to esketamine, propofol, or other medications in the trial; use of glucocorticoids or immunosuppressive agents within 1 month prior to surgery, or comorbid acute infections (C-reactive protein [CRP]>10 mg/L); preoperative presence of uncontrolled hypertension (>95th percentile for age) or severe cardiac arrhythmias (eg, ventricular tachycardia); history of epilepsy, mental retardation, or cognitive dysfunction; use of analgesic medication 24 hours before surgery; or guardian refusal to participate in the study. There were no participant dropouts or missing data points for any predefined endpoints among the 90 children who constituted the three study cohorts, ensuring a complete analysis. Therefore, no data imputation was necessary, and the analysis was performed on a complete dataset. The design procedure is shown in Figure 1.

Anesthesia Methods

Before the operation, children were forbidden to eat solid food for 6 hours and clear drinks for 2 to 3 hours. Atropine (manufacturer: Tianjin Jinyao Pharmaceutical Co., Ltd., China) 0.01 mg/kg was injected intramuscularly 30 minutes before the operation, and an intravenous infusion channel was established in the ward, and electrocardiogram, MAP, peripheral oxygen saturation (SpO_2), and bispectral index (BIS) etc., were monitored. Anesthesia induction: 0.25 mg/kg of esketamine (brand name: Ruikexin, manufacturer: Jiangsu Hengrui Medicine Co., Ltd., China) in the low-dose LD group, 0.5 mg/kg of esketamine in the medium-dose MD group, and 1 mg/kg of esketamine in the high-dose HD group, 3 mg/kg of propofol (brand name: Diprivan, original manufacturer: AstraZeneca, United Kingdom; distributed by Aspen Pharma Trading Limited) was given to each group, and after the children's eyelash reflex disappeared, cisatracurium (brand name: Nimbex; manufacturer: GlaxoSmithKline [GSK], United Kingdom) was given intravenously at 0.15 mg/kg. LD group: Esketamine was administered at 0.25 mg/(kg·h). MD group: The infusion rate was set at 0.5 mg/(kg·h). HD group: Patients received esketamine at 1 mg/(kg·h). All pediatric subjects were maintained under anesthesia with a continuous propofol infusion (5–8 mg/[kg·h]). The ventilator was configured with a tidal

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volume of 6 to 8 mL/kg and an inspiratory-to-expiratory (I:E) ratio of 1:2. The respiratory rate was titrated to maintain end-tidal carbon dioxide ($PETCO_2$) within 35 to 45 mm Hg (1 mm Hg≈0.133 kPa), while the BIS was kept between 40 and 60. After the completion of surgery, the pumping of general anesthesia drugs was stopped, the child opened his eyes or was called to open his eyes independently, and after the recovery of independent respiration, the endotracheal tube was removed, and the child was sent to the post-anesthesia care unit (PACU) for observation. If the agitation score during recovery was≥10 or the postoperative pain score was>5, propofol 1 mg/kg was injected intravenously and reassessed after 5 minutes of administration, and additional medication could be administered if necessary.

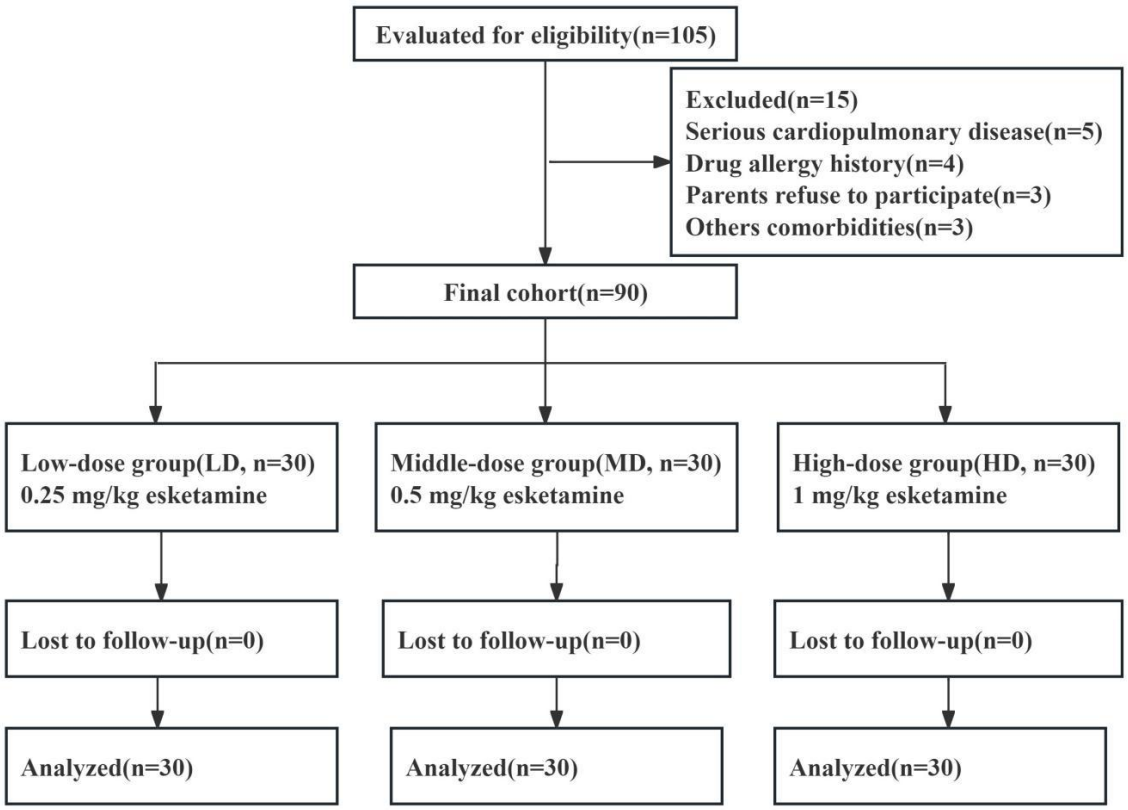

Figure 1. Flow chart of the study.

Observation Indicators

The primary outcome was the serum level of IL-6 at 1 hour postoperatively. Secondary outcomes included other inflammatory and immune markers (TNF-α, CRP, $CD4^+/CD8^+$ ratio, IgA, IgG), hemodynamic parameters, postoperative recovery scores (PAED, Face, Legs, Activity, Cry, Consolability (FLACC)), and the incidence of adverse events.

General Information

Includes demographic characteristics, clinical characteristics, preoperative vital signs, and preoperative laboratory indicators.

Hemodynamics

Hemodynamic parameters, including MAP, HR, and SpO_2, were monitored at five key time points: baseline (T_0, preoperative), intubation (T_1), 10 minutes post-incision (T_2), 30 minutes intraoperatively (T_3), and extubation (T_4).

Autoimmune Inflammation

Blood sampling was conducted preoperatively (T_0), 1 hour (T_1), and 24 hours (T_2) post-surgery. Serum samples destined for analysis of IL-6, TNF-α, CRP, IgA, and IgG underwent clotting (30 minutes, room temperature) and centrifugation (3000 rpm, 15 minutes)

before being aliquoted and stored at −80°C. EDTA-anticoagulated blood for flow cytometry was processed within 4 hours. Analytical methods included ELISA for IL-6 and TNF-α (kits from R&D Systems, USA), immunoturbidimetry for CRP/IgA/IgG (kits from Siemens Healthineers, Germany), and flow cytometric immunophenotyping for T cell subsets. The latter utilized a BD Multitest antibody panel (CD3/CD4/CD8/CD45; manufacturer: Becton, Dickinson and Company [BD], USA) and a BD FACS Canto II cytometer (BD, USA). After gating on the lymphocyte population via forward/side scatter, $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells were quantified to calculate the $CD4^+/CD8^+$ ratio.

Postoperative Recovery

Postoperative agitation was evaluated using the PAED scale at three postoperative intervals: 10 minutes, 30 minutes, and 1 hour following extubation. The scale includes 5 items of the child's eye contact, purposeful movements, state of consciousness, degree of agitation, and need for reassurance. Each item is scored from 0 to 4, and the higher the total score, the more severe the agitation, PAED≥10 points are considered as the occurrence of agitation.[17] The postoperative pain score FLACC was used to score the occurrence of pain at 1, 6, and 12 hours postoperatively, the FLACC scale includes 5 items for scoring facial expression, leg movement, mobility, crying, and soot ability, 0 to 2 points for each item, The scale yields a total score ranging from 0 to 10 points, where a lower score is inversely correlated with the quality of analgesia, indicating a superior outcome.[18]

Adverse Reaction

Nausea and vomiting, respiratory depression (SpO_2 <92% for 1 minute), delirium (CAM-ICU scale), and delayed awakening (time to awaken >30 minutes).

Sample Size Calculation

Based on a previous pediatric study by Zhu et al[19] reporting a moderate effect size (f=0.5) for IL-6 levels at 1-hour post-adenotonsillectomy across esketamine dose groups, we estimated the required sample size using G*Power. With the alpha level set at 0.05 and power (1−β) at 0.8. This computation indicated that a total sample size of 75 (25 per group) was necessary. The study successfully recruited a total of 90 subjects, allocating 30 to each group, thereby surpassing the pre-determined statistical requirement.

Statistical Analysis

SPSS 25.0 statistical software was used to analyze the data, and Lucidchart was used to draw flow charts. The data in this study were tested for normal distribution. Continuous variables including hemodynamic parameters (MAP, HR, SpO_2), cytokine levels (IL-6, TNF-α), acute-phase reactants (CRP), immune function markers ($CD4^+/CD8^+$, IgA, IgG), and recovery indices were summarized as mean ± standard deviation. Categorical data were reported as proportions (%). Comparisons of normally distributed continuous measures across the three groups at individual time points were performed with one-way ANOVA, with Tukey's HSD test applied for post-hoc analyses following a significant overall F-test. Longitudinal data (eg, hemodynamic trends) were evaluated using two-way repeated-measures ANOVA, also with Tukey's post-hoc testing. Group differences for categorical variables were assessed with the Chi-square test or Fisher's exact test, as warranted. A two-tailed p value<0.05 defined statistical significance.

RESULTS

Comparison of Baseline Information

The baseline data of the three groups of children showed no significant differences between the three groups in terms of demographic characteristics, clinical characteristics, preoperative vital signs, and preoperative laboratory indices (p>0.05), demonstrating that the three pediatric cohorts were well-balanced in their baseline demographic and clinical characteristics. See Table 1.

Hemodynamic Changes

Preoperatively, MAP, HR, and SpO_2 were comparable across all groups (p>0.05). At T_1, the LD regimen resulted in a MAP that fell significantly below its baseline value (p<0.05). Conversely, mean arterial pressure in the MD and HD groups remained stable and significantly superseded the levels measured in the LD group (p<0.05). This indicates that 0.5 mg/kg and 1.0 mg/kg esketamine effectively attenuated intubation-induced hypotension. HR was elevated in the LD group (p<0.05) but significantly lower in the MD group (p<0.05), suggesting that the intermediate dose better suppressed stress-induced tachycardia during intubation. During the T_2–T_3 interval, the MD group demonstrated HR values that remained closer to baseline

and were significantly lower than the elevated levels seen in the LD group (p<0.05). A mild increase in MAP was noted in the HD group, though the difference from the MD group was not statistically significant. This supports the conclusion that a dose of 0.5 mg/kg esketamine was adequate to maintain circulatory stability during surgery. At the T_4 time point, MAP and HR in both the LD and HD groups were significantly elevated above their baseline levels (p<0.05). In contrast, the MD group's readings most closely approximated baseline, implying that the intermediate dose most effectively blunted the cardiovascular stress response upon emergence. Perioperative SpO_2 remained stable (>97.5%) across all groups, with no intergroup differences (p>0.05). Overall, the MD group (0.5 mg/kg) demonstrated superior hemodynamic modulation compared to both lower and higher doses. See Table 2.

Table 1. Comparison of baseline characteristics of children in three groups.

Characteristic	LD Group (n=30)	MD Group (n=30)	HD Group (n=30)	Statistic	*p*
Demographic characteristics					
Age, y	5.2 ± 1.3	5.5 ± 1.6	5.3 ± 1.4	F=0.38	0.723
Sex (M/F)	18/12	16/14	17/13	χ^2=0.24	0.887
Weight, kg	19.6 ± 3.8	20.1 ± 4.2	19.9 ± 3.5	F=0.11	0.883
BMI, kg/m²	15.8 ± 1.6	16.1 ± 1.9	15.9 ± 1.7	F=0.22	0.800
ASA classification (I/II)	22/8	24/6	23/7	χ^2=0.31	0.856
Diagnostic trait					
Surgical time, min	35.6 ± 8.2	33.9 ± 7.8	34.7 ± 9.1	F=0.35	0.708
Anesthesia time, min	48.3 ± 10.5	46.7 ± 9.8	47.5 ± 11.2	F=0.18	0.839
Preoperative vital signs					
MAP, mm Hg	72.3 ± 6.5	70.8 ± 7.1	71.6 ± 6.8	F=0.42	0.630
HR, cycles/min	108 ± 12	105 ± 11	106 ± 13	F=0.57	0.622
SpO_2, %	98.2 ± 0.8	98.5 ± 0.7	98.3 ± 0.9	F=0.91	0.258
Preoperative laboratory indicators					
IL-6, pg/mL	8.2 ± 2.1	7.9 ± 1.8	8.3 ± 2.3	F=0.28	0.819
TNF-α, pg/mL	12.5 ± 3.4	13.1 ± 3.7	12.8 ± 3.2	F=0.19	0.918
CRP, mg/L	2.1 ± 0.7	2.3 ± 0.6	2.2 ± 0.8	F=0.33	0.276
$CD4^+/CD8^+$ ratio	1.6 ± 0.3	1.5 ± 0.4	1.6 ± 0.3	F=0.75	0.266
IgA, g/L	1.2 ± 0.4	1.3 ± 0.3	1.1 ± 0.5	F=0.61	0.219
IgG, g/L	9.8 ± 1.2	10.1 ± 1.4	9.6 ± 1.3	F=0.28	0.793

[a]ASA: American Society of Anesthesiologists; BMI: body mass index; CD: cluster of differentiation; CRP: C-reactive protein; HD: high-dose; HR: heart rate; Ig: immunoglobulin; IL: interleukin; LD: low-dose; MAP: mean arterial pressure; MD: medium-dose; SpO_2: peripheral oxygen saturation; TNF: tumor necrosis factor.

Table 2. Comparison of hemodynamics among the three groups of children at each time point.

Time Point	Parameter	LD Group (n=30)	MD Group (n=30)	HD Group (n=30)	Effect Size (η^2)	*p*
T_0	MAP, mm Hg	72.3 ± 5.1	73.1 ± 4.8	71.8 ± 5.6	0.012	0.630
	HR, cycles/min	98.5 ± 10.2	96.7 ± 9.8	99.3 ± 11.1	0.011	0.622
	SpO_2, %	98.5 ± 0.7	98.7 ± 0.6	98.4 ± 0.8	0.029	0.258
T_1	MAP, mm Hg	68.2 ± 6.3[b]	74.5 ± 5.1[c]	76.8 ± 4.9[c]	0.254	<0.001
	HR, cycles/min	112.4 ± 12.5[b]	101.6 ± 10.2[c]	105.3 ± 11.7[c]	0.118	0.002
	SpO_2, %	97.8 ± 1.1	98.3 ± 0.9	98.1 ± 1.0	0.034	0.166
T_2	MAP, mm Hg	70.5 ± 5.9	72.9 ± 4.7	74.2 ± 5.3[c]	0.081	0.070
	HR, cycles/min	105.7 ± 11.3	99.5 ± 11.0[c]	100.2 ± 10.5	0.083	0.061
	SpO_2, %	98.0 ± 0.9	98.5 ± 0.7	98.2 ± 0.8	0.049	0.381
T_3	MAP, mm Hg	71.8 ± 5.5	73.6 ± 4.9	75.1 ± 5.3[c]	0.068	0.061
	HR, cycles/min	104.3 ± 10.9	98.3 ± 9.5[c]	102.5 ± 11.0	0.074	0.088
	SpO_2, %	97.9 ± 1.0	98.4 ± 0.8	98.0 ± 0.9	0.041	0.328
T_4	MAP, mm Hg	75.6 ± 6.2[b]	72.8 ± 5.4[c]	78.1 ± 5.9[b,c]	0.237	0.002
	HR, cycles/min	118.9 ± 13.1[b]	104.2 ± 10.8[c]	110.5 ± 12.3[b,c]	0.201	<0.001
	SpO_2, %	97.5 ± 1.3	98.1 ± 1.0	97.9 ± 1.2	0.032	0.146

[a]Data are presented as mean ± SD. Single factor analysis of variance and Tukey post hoc test. The effect size (η^2) was calculated by ANOVA, $\eta^2 \geq 0.01$ was considered as small effect, ≥0.06 was considered as medium effect, and ≥0.14 was considered as large effect. T_0: preoperative; T_1: at intubation; T_2: 10 minutes intraoperatively; T_3: 30 minutes intraoperatively; T_4: at extubation. [b]Statistically meaningful differences versus T_0 (p<0.05). [c]Statistically meaningful differences versus the LD group (p<0.05). [d]HD: high-dose (1 mg/kg); HR: heart rate; LD: low-dose (0.25 mg/kg); MAP: mean arterial pressure; MD: medium-dose (0.5 mg/kg); SpO_2: peripheral oxygen saturation.

Immune-inflammatory Response

At T_0, no significant differences were observed in any inflammatory or immune parameters among the three groups (all p>0.05, Figure 2A–F). At T_5, both the MD and HD groups showed significantly lower levels of IL-6, TNF-α, and CRP than the LD group (all p<0.05), with the MD group exhibiting the most marked suppression of IL-6 and CRP. Concurrently, the MD group displayed a higher $CD4^+/CD8^+$ ratio and better-preserved IgA levels relative to the LD group (p<0.05), indicating attenuated T-cell immunosuppression and mucosal immune protection. By T_6, IL-6 and CRP levels remained lower in the MD group compared to the LD group (p<0.05), with no significant difference from the HD group. The $CD4^+/CD8^+$ ratio in the MD group recovered to 1.5 ± 0.2, significantly higher than that in the LD group, and IgA levels were maintained near the normal range. In contrast, IgG did not differ significantly across groups. These results suggest that 0.5 mg/kg esketamine provides optimal immunomodulation, effectively controlling inflammatory responses and supporting early immune recovery without broadly affecting systemic humoral immunity. Detailed data are presented in Table 3.

Table 3. Comparison of immune-inflammatory response at each time point among the three groups of children.

Parameter	Time Point	LD Group (n=30)	MD Group (n=30)	HD Group (n=30)	Effect Size (η^2)	*p*
IL-6, pg/mL	T_0	15.2 ± 3.1	14.9 ± 2.8	15.1 ± 3.0	0.003	0.918
	T_5	38.5 ± 4.2[b]	24.2 ± 3.8[c]	22.5 ± 3.6[c]	0.702	<0.001
	T_6	30.1 ± 3.8[b]	18.6 ± 2.9[c]	17.3 ± 2.7[c]	0.645	<0.001
TNF-α, pg/mL	T_0	8.5 ± 1.2	8.4 ± 1.1	8.6 ± 1.3	0.005	0.819
	T_5	12.3 ± 1.5[b]	9.8 ± 1.2[c]	9.5 ± 1.1[c]	0.521	<0.001
	T_6	10.2 ± 1.3[b]	8.9 ± 1.0[c]	8.7 ± 0.9[c]	0.388	<0.001
CRP, mg/L	T_0	2.1 ± 0.5	2.0 ± 0.4	2.2 ± 0.6	0.031	0.276
	T_5	8.7 ± 1.2[b]	5.3 ± 0.8[c]	4.9 ± 0.7[c]	0.735	<0.001
	T_6	12.5 ± 2.1[b]	7.8 ± 1.3[c]	7.5 ± 1.2[c]	0.692	<0.001
$CD4^+/CD8^+$	T_0	1.5 ± 0.3	1.6 ± 0.2	1.5 ± 0.3	0.033	0.266
	T_5	1.1 ± 0.2[b]	1.4 ± 0.2[c]	1.3 ± 0.2[c]	0.452	<0.001
	T_6	1.3 ± 0.3[b]	1.5 ± 0.2[c]	1.4 ± 0.3	0.128	0.015
IgA, g/L	T_0	1.2 ± 0.3	1.3 ± 0.2	1.2 ± 0.3	0.035	0.219
	T_5	0.9 ± 0.2[b]	1.1 ± 0.2[c]	1.0 ± 0.2	0.185	0.001
	T_6	1.0 ± 0.2[b]	1.2 ± 0.3[c]	1.1 ± 0.2	0.142	0.008
IgG, g/L	T_0	8.5 ± 1.1	8.6 ± 1.0	8.4 ± 1.2	0.008	0.793
	T_5	7.9 ± 1.0	8.2 ± 0.9	8.0 ± 1.1	0.023	0.514
	T_6	8.1 ± 0.9	8.4 ± 1.0	8.2 ± 1.0	0.024	0.489

[a]Data are presented as mean ± SD. Single factor analysis of variance and Tukey post hoc test. The effect size (η^2) was calculated by ANOVA, $\eta^2 \geq 0.01$ was considered as small effect, ≥0.06 was considered as medium effect, and ≥0.14 was considered as large effect. T_0: preoperative; T_5: 1 hour postoperative; T_6: 24 hours postoperative.

[b]Statistically meaningful differences versus T_0 ($p<0.05$).

[c]Statistically meaningful differences versus the LD group ($p<0.05$).

[d]CD: cluster of differentiation; CRP: C-reactive protein; HD: high-dose (1 mg/kg); Ig: immunoglobulin; IL: interleukin; LD: low-dose (0.25 mg/kg); MD: medium-dose (0.5 mg/kg); TNF: tumor necrosis factor.

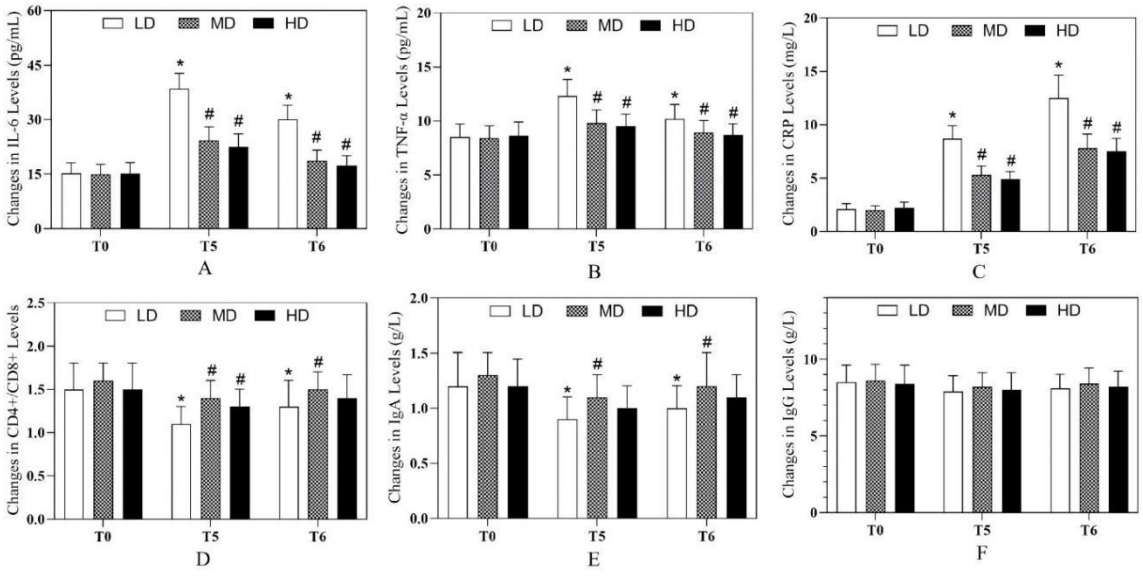

Figure 2. Comparison of immune-inflammatory response at each time point among the three groups of children. A, IL-6; B, TNF-α; C, CRP; D, $CD4^+/CD8^+$; E, IgA; F, IgG. LD indicates low-dose (0.25 mg/kg); MD, medium-dose (0.5 mg/kg); HD, high-dose (1 mg/kg) esketamine; T_0, preoperative; T_5, 1 hour postoperative; T_6, 24 hours postoperative. Single factor analysis of variance and Tukey post hoc test: *reveals statistically meaningful differences versus T_0 (p<0.05); #reveals statistically meaningful differences versus the LD group (p<0.05).

Postoperative Recovery

The three groups were comparable in preoperative demographics and surgical duration (p>0.05). At 10 minutes post-extubation, the LD group showed significantly higher PAED scores (≥12) than the MD and HD groups (p<0.05), which did not differ from each other, indicating moderate-to-severe EA. These results demonstrate that 0.5 mg/kg esketamine effectively prevents early postoperative agitation. 30 to 60 minutes post-extubation, the MD group maintained superior agitation control, with scores progressively declining to near-normal ranges (PAED ≤3) by 60 minutes, significantly outperforming the LD group (p<0.05). This suggests enhanced quality of emergence and faster neurological recovery with the intermediate dose. 1 hour postoperative, FLACC pain scores in the MD group were significantly reduced compared to LD controls (p<0.05), while remaining comparable to HD values. This indicates that 0.5 mg/kg provides sufficient acute postoperative analgesia. 6 to 12 hours postoperative, the MD regimen demonstrated sustained analgesic superiority, with scores approaching pain-free thresholds (FLACC≤1) by 12 hours-significantly better than LD outcomes (p<0.05). These findings position the intermediate dose as optimal for prolonged postoperative pain management. The HD group showed no further improvement in pain scores, suggesting that there was no clinical benefit from the additional dose. Thus, the medium-dose group (0.5 mg/kg) was superior to the low- and high-dose groups in terms of rapid postoperative sedation and long-lasting analgesia. See Table 4.

Adverse Reaction

The total incidence of adverse reactions was 30.00%, 4.00% and 13.00% in LD, MD and HD groups, respectively, with the highest incidence of nausea and vomiting in the HD group and the lowest in the MD group, suggesting that 0.5 mg/kg balances the intensity of analgesia with gastrointestinal tolerance. Respiratory depression occurred only in the LD and HD groups, with no cases in the MD group, suggesting that the mid-dose had the least effect on respiratory drive. The incidence of delirium and delayed awakening was the highest in the HD group and the lowest in the MD group, reflecting that the medium dose could realize the precise regulation of neural excitability. The total adverse incidence rate in the MD group was significantly lower than that in the LD group and the HD group (p<0.05), suggesting that the safety profile of 0.5 mg/kg of esketamine was superior. See Table 5.

Table 4. Comparison of postoperative recovery of children in three groups.

Score	Time Point	LD Group (n=30)	MD Group (n=30)	HD Group (n=30)	Effect Size (η^2)	*p*
PAED score	10 minutes after extubation	12.5 ± 2.8[b]	6.3 ± 1.5[c]	7.1 ± 1.8[c]	0.721	<0.001
	30 minutes after extubation	10.2 ± 2.3[b]	4.7 ± 1.2[c]	5.3 ± 1.4[c]	0.698	<0.001
	1 hour after extubation	7.8 ± 1.9[b]	3.1 ± 0.9[c]	3.5 ± 1.1[c]	0.662	<0.001
FLACC score	1 hour after surgery	4.5 ± 1.2[b]	2.1 ± 0.8[c]	2.3 ± 0.9[c]	0.612	<0.001
	6 hours after surgery	3.8 ± 1.0[b]	1.7 ± 0.6[c]	1.9 ± 0.7[c]	0.588	<0.001
	12 hours after surgery	2.9 ± 0.8[b]	1.2 ± 0.5[c]	1.4 ± 0.6[c]	0.543	<0.001

[a]Data are presented as mean ± SD, one-way ANOVA with Tukey post hoc test. The effect size (η^2) was calculated by ANOVA, $\eta^2 \geq 0.01$ was considered as small effect, ≥0.06 was considered as medium effect, and ≥0.14 was considered as large effect.
[b]Statistically meaningful differences versus the MD group ($p<0.05$).
[c]Statistically meaningful differences versus the LD group ($p<0.05$).
[d]FLACC: Face, Legs, Activity, Cry, Consolability; HD: high-dose (1 mg/kg); LD: low-dose (0.25 mg/kg); MD: medium-dose (0.5 mg/kg); PAED: Pediatric Anesthesia Emergence Delirium.

Table 5. Incidence of adverse reactions.

Group	Nausea and Vomiting, n (%)	Respiratory Depression, n (%)	Delirium, n (%)	Delayed Awakening, n (%)	Total Adverse Reaction Rate, n (%)
LD group (n=30)	4 (13.33)	1 (3.33)	2 (6.67)	2 (6.67)	9 (30.00)
MD group (n=30)	2 (6.67)	0 (0.00)	1 (3.33)	1 (3.33)	4 (13.33)
HD group (n=30)	5 (16.67)	2 (6.67)	3 (10.00)	3 (10.00)	13 (43.33)
χ^2	4.28	3.12	2.75	3.45	8.91
p Value	0.12	0.21	0.25	0.18	<0.05

HD: high-dose (1 mg/kg); LD: low-dose (0.25 mg/kg); MD: medium-dose (0.5 mg/kg).

DISCUSSION

This retrospective study demonstrated the superior efficacy of 0.5 mg/kg esketamine over both lower (0.25 mg/kg) and higher (1.0 mg/kg) doses in pediatric adenotonsillectomy, evidenced by enhanced hemodynamic stability, a more favorable immune-inflammatory profile, improved recovery quality, and the lowest incidence of adverse events. These collective findings position this intermediate dose as the optimal regimen for maximizing the benefit-risk ratio in this surgical context.

When the body is subjected to external injurious stimuli, self-protective mechanisms are activated, resulting in hemodynamic abnormalities. MAP and HR are commonly used in clinical assessment of hemodynamics.[20] At notable perioperative stress periods (T_1, T_4), the intermediate 0.5 mg/kg esketamine dose

provided more effective suppression of HR and MAP fluctuations than either the low (0.25 mg/kg) or high (1 mg/kg) dose. Esketamine produces analgesia by blocking NMDA receptors and activating opioid receptors, while enhancing sympathetic activity by inhibiting norepinephrine reuptake.[21,22] We speculate that 0.5 mg per kilogram may be a critical balance: it provides sufficient analgesia to suppress the stress response without having a sympathetic activating effect such that it triggers substantial tachycardia or hypertension. This is consistent with literature reports that low doses may lead to compensatory cardiovascular excitation due to inadequate analgesia, whereas high doses may have destabilizing effects due to sympathetic hyperactivation or direct myocardial depression.[23] The retrospective nature of this study means that dose selection was not random and may have been influenced by the anesthesiologist's clinical judgment of the patient's condition. The clear dose-response relationship observed, however, strongly supports the superiority of the intermediate dose in hemodynamic management.

Tonsils and adenoids, as important immune organs of the upper respiratory tract in children, play a central role in systemic and mucosal immunity.[24,25] One of the core findings of this study was that 0.5 mg/kg dose was most effective in suppressing the postoperative increase in IL-6 and CRP and promoting the recovery of $CD4^+/CD8^+$ ratio and IgA levels, suggesting the existence of an immunomodulatory "therapeutic window." The underlying mechanisms may go beyond simple analgesia. Existing studies have shown that the anti-inflammatory effect of esketamine may be related to the inhibition of NF-κB signaling pathway, thereby reducing the release of proinflammatory factors such as IL-6 and TNF-α.[26–29] Although the molecular pathways involved were not directly examined in this study, the observed changes in inflammatory factors are consistent with such a mechanism. In addition, esketamine may maintain immune balance by regulating the function of T cell subsets, inhibiting the over-activation of $CD8^+$ T cells and promoting the differentiation of $CD4^+$ T cells to an anti-inflammatory phenotype[30,31]; ketamine's influence on immune function is dual-natured, and the "optimal effect" presented by the dose in this study is consistent with reports that lower doses may transiently activate the TLR4 pathway, while higher doses may cause immunosuppression.[32,33] However, one limitation of the present analysis was the absence of data on anti-inflammatory mediators, including IL-10; future studies incorporating such measures would be useful to assess immune balance more fully.

Postoperative pain is a common problem faced by surgical patients, and perfect analgesia is conducive to patients' postoperative recovery. As an NMDA receptor antagonist, esketamine exhibits dual analgesic and sedative properties.[34] In this study, the medium-dose regimen demonstrated superior postoperative outcomes, with significantly lower PAED and FLACC scores than the low-dose group. While achieving a comparable quality of recovery to the high-dose group, the medium dose was associated with a significantly lower overall incidence of adverse effects. This is consistent with the pharmacological properties of esketamine, whose potent analgesic effect reduces nociceptive stimulus afferents that cause agitation and pain at the source. This finding is consistent with the conclusion of a recent multicenter study, which found that medium-dose esketamine is the appropriate dose for reducing postoperative pain sensitivity, compared with low and high doses, without increasing adverse effects.[35] Thus, from a benefit-risk perspective, 0.5 mg/kg of esketamine represents a balanced clinical choice, providing superior pain relief in pediatric patients while avoiding an increase in agitation and demonstrating an excellent safety outcome.

Placing the findings of this study in the clinical context of pediatric anesthesia and comparing them with other drugs with immunomodulatory potential, such as dexmedetomidine and propofol, will help clarify the unique value of esketamine. Although dexmedetomidine has good sedative and anxiolytic effects and can exert partial anti-inflammatory effects by inhibiting sympathetic nerves, its potent analgesic effect is insufficient, and it carries the risk of bradycardia and hypotension.[36] Although propofol has certain anti-inflammatory properties, its immunomodulatory effects are relatively weak and its respiratory and circulatory inhibitory effects are significant.[37] In contrast, esketamine showed a multi-dimensional synergistic effect of "analgesia, sedation, anti-inflammation, and hemodynamic stabilization." This "multiple in one" mode of action makes it show a unique comprehensive advantage in short surgery such as tonsillectomy and adenoidectomy, which is highly stimulating and easy to cause immune and inflammatory disorders, especially for patients with OSAS and sensitive to respiratory depression.

The present study confirms the significant advantages of 0.5 mg/kg esketamine in adenotonsillectomy in children through a multidimensional assessment: it maintains hemodynamic stability by balancing sympathetic activation and myocardial inhibition, protects immune function by dynamically modulating the inflammatory response, and improves the quality of recovery by optimizing the analgesic-sedative balance. This dosage regimen provides high-quality evidence for the management of anesthesia in children undergoing short-term surgery and is worthy of clinical dissemination. Despite the meaningful results of this study, there are several limitations: First, due to the single-center retrospective study design and relatively small sample size, confounding bias cannot be completely ruled out, and the external validity of these findings may be constrained. Second, the immunologic indexes at 24 hours postoperatively failed to reflect long-term immune function changes, which is still insufficient for assessing long-term efficacy and safety. Third, we did not measure anti-inflammatory factors such as IL-10, which limits the full interpretation of the immune balance. Finally, the fixed dosing regimen of co-administered propofol, while standardizing the anesthetic depth, could be a confounding factor in assessing the pure immunomodulatory effects of esketamine. In the future, larger sample size, longer follow-up (eg, 72 hours or 7 days) and more comprehensive immune indicators are needed to validate the findings of this study and further explore individualized treatment regimens.

STATEMENT OF ETHICS

This study received ethics approval from the Ethics Committee of Baoding Second Central Hospital (approval number: 2023-43), complying with the Declaration of Helsinki and international standards for medical research ethics. On account of the retrospective study design, the analysis was based on previous clinical archived data, and the ethics committee has approved the exemption of informed consent. All study data were anonymized to ensure the privacy and identity of the participants.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request. Patient privacy and institutional confidentiality are protected.

AI ASSISTANCE DISCLOSURE

None declared.

REFERENCES

1. Nguyen BK, Quraishi HA. Tonsillectomy and Adenoidectomy - Pediatric Clinics of North America. Pediatr Clin North Am. 2022;69(2):247-59.
2. Mion G, Himmelseher S. Esketamine: Less Drowsiness, More Analgesia. Anesth Analg. 2024;139(1):78-91.
3. Wang J, Feng Y, Qi Z, Li J, Chen Z, Zhang J, et al. The role and mechanism of esketamine in preventing and treating remifentanil-induced hyperalgesia based on the NMDA receptor-CaMKII pathway. Open Life Sci. 2024;19(1):20220816.
4. Cao Y, Song Y, Wang Z, Tang J, Yi J, Liu Y, et al. Effects of different dosages esketamine on cardiac conduction and heterogeneity of Cx43: the epicardial mapping in guinea pigs. Ann Transl Med. 2022;10(14):772.
5. Weiyun S, Yan Y, Wenjuan Z, Junmei X, Zhijian L, Lin Y. Esketamine mitigates systemic inflammation via modulating phenotypic transformation of monocytes in patients undergoing thoracic surgery. Life Sci. 2025;371:123594.
6. Fageeh YA. Clinical Impact of Preoperative Tonsil and Adenoid Size on Symptomatic Outcomes Following Adenotonsillectomy in Pediatric Patients. Cureus. 2023;15(10):e47093.
7. Proshad NE, Pedro P, Jenny P, Kiley FP, Ron BM, Peter S. Pediatric obstructive sleep apnea: a prospective observational study of respiratory events in the immediate recovery period after adenotonsillectomy. Anaesth Crit Care Pain Med. 2024;43(4):101385.

8. Ayuko I. Extubation and removal of supraglottic airway devices in pediatric anesthesia. Anesthesia and Pain Medicine. 2024;19.
9. Ramy M, Mohammed Sayed S, Amr AK. Opioid Free Ptyregopalatine Ganglion Block Based Multimodal Anesthesia Versus Conventional Opioid Based Multimodal Anesthesia for Tonsillectomy Operations: A Randomized Controlled Trial. Anesthesiology and Pain Medicine. 2024;14(3).
10. Passaint FH, Amany HS. Comparison of dexmedetomidine, ketamine, and magnesium sulfate for the prevention of emergence agitation following sevoflurane-based anesthesia in pediatric cardiac catheterization. Minerva Anestesiologica. 2025;91(3).
11. Liao Y, Xie S, Zhuo Y, Chen S, Luo Y, Wei Y, et al. 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 design, development and therapy. 2024;18:4693-703.
12. Wang Y, Ma B, Wang C, Wang Y, Liu A, Hang L. The influence of low-dose s-ketamine on postoperative delirium and cognitive function in older adults undergoing thoracic surgery. J Cardiothorac Surg. 2024;19(1):324.
13. Wakabayashi N, Watanabe S, Abe T, Takenaka J, Hirata K, Kimura R, et al. Safety and efficacy of multiple-dose versus single-dose MIBG therapy in patients with refractory pheochromocytoma and paraganglioma: a single-center retrospective analysis. Ann Nucl Med. 2024;38(7):553-62.
14. Jung KW, Kim WJ, Jeong HW, Kwon HM, Moon YJ, Jun IG, et al. Impact of Inhalational Anesthetics on Liver Regeneration After Living Donor Hepatectomy: A Propensity Score-Matched Analysis. Anesth Analg. 2018;126(3):796-804.
15. Ye T, Zhang N, He Y, Chen C, Zha Q, Zhang A, et al. Electroacupuncture pretreatment inhibits the TLR4/NF-κB/TXNIP/NLRP3 signaling pathway and modulates microglial polarization to alleviate cerebral ischemia-reperfusion injury in rats. Neuroscience. 2024;562:33-42.
16. Singh I, Kim J, Touhidul Islam SM, Fei Q, Singh AK, Won J. The role of S-nitrosoglutathione reductase (GSNOR) in T cell-mediated immunopathology of experimental autoimmune encephalomyelitis (EAE). Neuroscience. 2025;564:1-12.
17. Ringblom J, Wåhlin I, Proczkowska M, Korhonen L, Årestedt K. Measurement Properties of the Pediatric Anesthesia Emergence Delirium Scale: A Confirmatory Factor Analysis-Based Study. Paediatr Anaesth. 2025;35(2):155-62.
18. Manworren RC, Hynan LS. Clinical validation of FLACC: preverbal patient pain scale. Pediatr Nurs. 2003;29(2):140-6.
19. Zhu Y, Wang X, Wang L, Zhang Y. Effects of esketamine on postoperative pain and inflammatory factors in children undergoing tonsillectomy and adenoidectomy. Minerva Anestesiol. 2025;91(1-2):18-25.
20. Ruíz-López P, Domínguez JM, Morgaz J, Quirós-Carmona S, Navarrete-Calvo R, Gómez-Villamandos RJ, et al. Evaluation of the averaged parasympathetic tone activity and its dynamic variation to assess intraoperative nociception in relation to hemodynamic changes in dogs. Vet Q. 2023;43(1):1-9.
21. Shamim M, Sepideh G, Razieh Mohammad J, Shafaroodi H, Dehpour A, Sanatkar M. The N-methyl-D-aspartate receptor antagonist ketamin exerts analgesic effects via modulation of the nitric oxide pathway. Fundamental Clin Pharmacol. 2022((6)):956-65.
22. Yang H, Zhao Q, Chen HY, Liu W, Ding T, Yang B, et al. The median effective concentration of propofol with different doses of esketamine during gastrointestinal endoscopy in elderly patients: A randomized controlled trial. Br J Clin Pharmacol. 2022;88(3):1279-87.
23. Ikeda S, Shinohara K, Kashihara S, Matsumoto S, Yoshida D, Nakashima R, et al. Esaxerenone: blood pressure reduction and cardiorenal protection without reflex sympathetic activation in salt-loaded stroke-prone spontaneously hypertensive rats. Hypertens Res. 2024;47(8):2133-43.
24. Zihui Y, Ziying X, Tongtong F, Shiyu L, Jinghua C, Bing Z, et al. Parallel comparison of T cell and B cell subpopulations of adenoid hypertrophy and tonsil hypertrophy of children. Nature Communications. 2025;16(1).
25. Xu Q, Milanez-Almeida P, Martins AJ, Radtke AJ, Hoehn KB, Oguz C, et al. Adaptive immune responses to SARS-CoV-2 persist in the pharyngeal lymphoid tissue of children. Nat Immunol. 2023;24(1):186-99.
26. Madi A, Weisshaar N, Buettner M, Poschet G, Ma S, Wu J, et al. CD8 agonism functionally activates memory T cells and enhances antitumor immunity. Int J Cancer. 2022;151(5):797-808.
27. Pracha SH, Shrestha S, Ryan N, Upadhaya P, Lamenza FF, Jagadeesha S, et al. Targeting macrophage migration inhibitory factor to inhibit T cell immunosuppression in the tumor microenvironment and improve cancer outcomes in

head and neck squamous cell carcinoma. Oral Oncol. 2025;160:107126.
28. Hanahan D, Michielin O, Pittet MJ. Convergent inducers and effectors of T cell paralysis in the tumour microenvironment. Nat Rev Cancer. 2025;25(1):41-58.
29. Wu W, Li Y, Wu X, Liang J, You W, He X, et al. Carnosic acid nanocluster-based framework combined with PD-1 inhibitors impeded tumorigenesis and enhanced immunotherapy in hepatocellular carcinoma. Funct Integr Genomics. 2024;24(1):5.
30. Qing X, Fengting Y, Liting Y, Xiaojie L, Xuelei L, Hongxin Z, et al. The CD4/CD8 ratio is associated with T lymphocyte functions in long-term virally suppressed patients with HIV. BMC Infectious Diseases. 2025;25(1).
31. Han J, Zhao L, Wu J, Diao Y, Guo Q, Yang J, et al. Role of CD4(+)T, CD8(+)T Cells, and CD4(+)T/CD8(+)T Cell Ratio in Gastric Cancer and Its Clinical Significance. Appl Bionics Biomech. 2022;2022:1094607.
32. Husien HM, Peng W, Essa MOA, Adam SY, Ur Rehman S, Ali R, et al. The Anti-Inflammatory Properties of Polysaccharides Extracted from Moringa oleifera Leaves on IEC6 Cells Stimulated with Lipopolysaccharide In Vitro. Animals (Basel). 2024;14(23).
33. Zhou X, Li Q, Luo Q, Wang L, Chen J, Xiong Y, et al. A single dose of ketamine relieves fentanyl-induced-hyperalgesia by reducing inflammation initiated by the TLR4/NF-κB pathway in rat spinal cord neurons. Drug Discov Ther. 2023;17(4):279-88.
34. Chen H, Zhi J, Wang L, Jin Z, Xu J, Xing F, et al. Subanesthetic Dose of Esketamine Improves the Sedative and Analgesic Effects of Dexmedetomidine and Remifentanil in Liposuction Anesthesia: A Prospective, Double-Blinded, Randomized Controlled Trial. Drug design, development and therapy. 2024;18:3645-58.
35. Ren YL, Yuan JJ, Xing F, Zhu LN, Zhang W. Effects of Different Doses of Esketamine on Pain Sensitivity of Patients Undergoing Thyroidectomy: A Randomized Controlled Trial. Pain Therapy. 2023;12(3):739-50.
36. He J, Lian X, Luo T. Evaluating dexmedetomidine in mitigating emergence agitation and perioperative complications in pediatric tonsillectomy and/or adenoidectomy: a systematic review and meta-analysis. Front Pharmacol. 2025;16:1681936.
37. Shen F, Zhang L, Wang X, Li B, Liu W, Xue Y, et al. Effect of Intravenous, Inhalational, or Combined Anesthesia Maintenance on Postoperative Respiratory Adverse Events in Children Undergoing Adenotonsillectomy (AmPRAEC): A Multicenter Randomized Clinical Trial. Anesthesiology. 2025;143(6):1484-96.