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CLINICAL TRIAL REPORT

Intranasal Esketamine Premedication Reduces Sevoflurane Requirements During Laryngeal Mask Airway Insertion in Pediatric Patients: A Randomized Controlled Trial

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Purpose: This study evaluated whether intranasal esketamine premedication reduces sevoflurane requirements for laryngeal mask airway (LMA) insertion in young children.

Patients and Methods: This randomized, double-blind, placebo-controlled trial enrolled 90 children (2–5 years) undergoing elective strabismus surgery. Participants received intranasal premedication with either saline (control), esketamine 0.5 mg/kg, or esketamine 1.0 mg/kg. The primary outcome was the minimum alveolar concentration of sevoflurane needed for successful LMA placement, determined using Dixon's up-and-down method. Secondary outcomes included anesthesia induction quality (4-point cooperation scale), emergence delirium (Pediatric Anesthesia Emergence Delirium scale), emergence time (from sevoflurane discontinuation to purposeful response), behavioral changes at day 3 (Post-Hospitalization Behavior Questionnaire), and adverse events.

Results: Intranasal esketamine produced dose-dependent reductions in sevoflurane requirements: 2.16 ± 0.18% (control), 1.87 ± 0.17% (0.5 mg/kg), and 1.50 ± 0.19% (1.0 mg/kg), representing decreases of 13.4% and 30.6%, respectively. The higher esketamine dose significantly improved induction quality (p=0.002), reduced emergence delirium (13.8% versus 46.4%, p=0.007), and decreased negative postoperative behavioral changes on day 3 (20.7% versus 53.6%, p=0.010). Emergence time and adverse event rates remained similar across groups.

Conclusion: Intranasal esketamine premedication effectively reduces sevoflurane requirements for LMA placement in children in a dose-dependent manner. The 1.0 mg/kg dose provides optimal clinical benefits without prolonging recovery or increasing complications. This approach offers pediatric anesthesiologists a practical method to reduce volatile anesthetic exposure while improving patient outcomes and potentially minimizing anesthetic-related risks.

Keywords: esketamine, premedication, sevoflurane, minimum alveolar concentration, laryngeal mask airway, pediatric anesthesia

Introduction

Pediatric anesthesia management requires balancing adequate anesthetic depth with minimal side effects. Sevoflurane remains the preferred inhalational agent in pediatric practice due to its favorable induction characteristics and low airway irritation potential. However, it may produce excitatory phenomena during the induction and emergence phases, particularly in younger children.[1] The laryngeal mask airway (LMA) has become integral to pediatric anesthesia,

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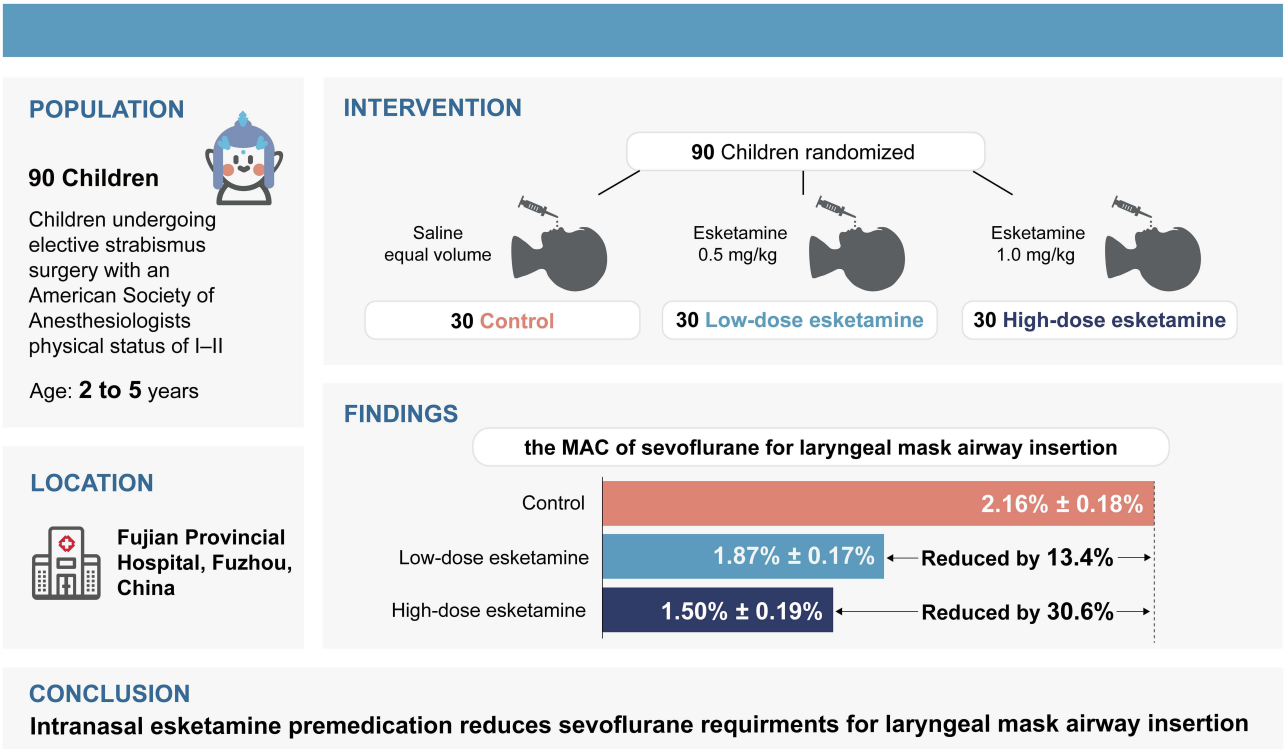
Graphical Abstract



facilitating spontaneous ventilation during general anesthesia for minor surgical procedures.[2] When insufficient anesthetic depth, LMA insertion can trigger significant protective airway reflexes, including laryngospasm and coughing.[3] While deepening anesthesia effectively prevents these airway responses, higher sevoflurane concentrations have been associated with adverse neurological effects in susceptible patients, including epileptiform activity and emergence agitation, though individual patient factors significantly influence risk.[4–6] Successful LMA placement therefore requires careful optimization of anesthetic depth, quantified as the minimum alveolar concentration required for LMA insertion (MAC_{LMA}).

Premedication offers several advantages in pediatric anesthesia, including anxiety reduction, improved induction cooperation, enhanced anesthetic potentiation, and decreased anesthetic requirements.[7,8] Studies have shown that midazolam and dexmedetomidine effectively reduce sevoflurane requirements for LMA insertion.[9,10] However, these agents present significant limitations: delayed onset, prolonged recovery times, and potential for paradoxical agitation or hemodynamic instability.

Esketamine, the S (+) enantiomer of ketamine, has emerged as a promising alternative for pediatric premedication.[11] This N-methyl-D-aspartate receptor (NMDA) antagonist exhibits approximately twice the analgesic potency of racemic ketamine with fewer psychological side effects, minimal secretions, rapid onset, and shorter recovery time.[12] Unlike conventional agents, esketamine preserves airway reflexes without causing cardiovascular depression. Intranasal administration is particularly suitable for pediatric patients as it avoids injection-related distress while ensuring efficient mucosal absorption.[13]

Despite these advantages, the effect of intranasal esketamine premedication on sevoflurane requirements for LMA insertion in pediatric patients has not been investigated. This randomized controlled trial, therefore, examines whether intranasal esketamine at doses of 0.5 mg/kg and 1.0 mg/kg reduces the minimum alveolar concentration of sevoflurane

required for LMA insertion in children undergoing elective strabismus surgery. We hypothesize that intranasal esketamine premedication will produce dose-dependent reductions in sevoflurane requirements, enabling adequate anesthetic depth at lower sevoflurane concentrations, thereby reducing risks associated with inadequate anesthesia and excessive volatile exposure.

Methods

Study Design and Participants

This randomized, double-blind, placebo-controlled trial was conducted at Fujian Provincial Hospital, China, from November 2023 through September 2024. The Institutional Review Board approved the study protocol (approval number K2023-01-003) on January 18, 2023, with trial registration at the Chinese Clinical Trials Registry (https://www.chictr.org.cn/showproj.html?proj=208297, ChiCTR2300076364) on October 7, 2023. Written informed consent was obtained from all parents or legal guardians before enrollment. The study adhered to the Declaration of Helsinki principles, Good Clinical Practice guidelines, and CONSORT 2025 reporting standards.[14]

We enrolled healthy children aged 2–5 years, classified as American Society of Anesthesiologists, with physical status I or II and scheduled for elective strabismus surgery, who were eligible for participation. We excluded patients with suspected difficult airway, recent respiratory conditions (within two weeks), recent sedative or analgesic use (within 48 hours), neuropsychiatric disorders, obesity (body mass index > 30 kg/m²), known allergies to study medications, or significant life events within one month of surgery (parental divorce, bereavement, relocation, or school changes) that might affect behavioral assessments.

Randomization and Allocation Concealment

Participants were randomly assigned in equal proportions (1:1:1) to one of three treatment groups using computer-generated randomization: control (saline), esketamine 0.5 mg/kg, or esketamine 1.0 mg/kg. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. An independent research pharmacist, isolated from the clinical team, prepared identical syringes labeled only with study codes on the day of surgery. This double-blind design was maintained throughout the trial, with parents/guardians, healthcare providers, and outcome assessors all blinded to treatment assignments.

Premedication Protocol

All premedications were administered in a designated preoperative area with parents present to reduce anxiety. Twenty minutes before anesthetic induction, participants received one of three intranasal treatments according to their randomization: 0.9% saline solution (control), esketamine 0.5 mg/kg, or esketamine 1.0 mg/kg. Each formulation was delivered at a standardized volume of 0.04 mL/kg using a 1-mL syringe. An independent nurse administered the medication by instilling equal volumes into each nostril while the child remained supine.

Anesthetic Management

Children followed standard fasting guidelines (6–8 hours for solids, 2 hours for clear liquids) before anesthesia.[15] Standard monitoring was established on arrival in the operating room, including pulse oximetry, electrocardiography, capnography, and noninvasive blood pressure measurement. We used a face mask with a semi-closed circuit system for anesthesia induction, delivering 5% sevoflurane in oxygen at 6 L/min. Ventilation progressed from initial spontaneous breathing to gentle manual assistance, maintaining end-tidal carbon dioxide between 35–45 mmHg throughout the procedure. We maintained the core temperature at 36.8 ± 0.4°C using a forced-air warming system (Bair Hugger 755; 3M Healthcare, USA). Sevoflurane concentration and end-tidal carbon dioxide were continuously monitored using a CARESCAPE Monitor B650 (GE Healthcare, USA).

Sevoflurane MAC_{LMA} Determination

We determined the minimum alveolar concentration of sevoflurane required for LMA insertion using Dixon's sequential up-and-down method.[16] Starting concentrations followed established protocols: 2.0% for the control group based on published data for unpremedicated children.[10] The esketamine groups began at lower concentrations (1.6% for 0.5 mg/kg and 1.2% for 1.0 mg/kg) reflecting the expected dose-dependent anesthetic-sparing effect of NMDA receptor antagonists. All concentrations were equilibrated for 15 minutes before LMA insertion to ensure steady-state conditions.

To ensure unbiased assessment, a single experienced pediatric anesthesiologist (with over 200 LMA insertions annually) performed all procedures while blinded to the premedication type and sevoflurane concentration. Following each insertion attempt, the sevoflurane concentration was adjusted by ± 0.2% for the next patient in that group. An unsuccessful insertion (intentional movement, coughing, or airway reaction within one minute of insertion) led to a 0.2% increase, while a successful insertion prompted a 0.2% decrease. Independent observers, also blinded to treatment allocation, documented all responses to maintain assessment objectivity.

Anesthesia and Recovery Protocol

Following LMA placement assessment, anesthesia was deepened with 2.0 mg/kg propofol, 0.2 μg/kg sufentanil, and 0.3 mg/kg rocuronium. Maintenance anesthesia consisted of 2% sevoflurane in a 50% oxygen-air mixture. Analgesia included 1 mg/kg intravenous flurbiprofen axetil and 0.4% oxybuprocaine eye drops administered perioperatively. Antiemetic prophylaxis comprised 0.15 mg/kg dexamethasone and 0.1 mg/kg ondansetron. Following surgery and LMA removal, children were transferred to the PACU, where parents provided emotional support during recovery.

Outcome Measures

The primary outcome was the MAC_{LMA} of sevoflurane, determined using Dixon's up-and-down sequential allocation method.[17] This method relies on identifying crossover events—instances where a patient's response differed from the preceding patient's response (either successful insertion followed by unsuccessful insertion or the reverse). We calculated each crossover value as the midpoint between the end-tidal sevoflurane concentrations. The final MAC_{LMA} for each group was derived by averaging all crossover values.

For secondary outcomes, we assessed anesthesia induction quality using a validated 4-point scale (1 = uncooperative behavior requiring physical restraint; 4 = full cooperation or sleep state with mask acceptance).[18] Emergence delirium was assessed during the first 30 minutes of recovery using the Pediatric Anesthesia Emergence Delirium scale, with scores ≥10 indicating clinically significant delirium.[19] Emergence time was defined as the interval from sevoflurane discontinuation to purposeful movement in response to verbal commands. Discharge readiness from the PACU was evaluated using the modified Aldrete scoring system (threshold ≥9).[20] Parental satisfaction was assessed 24 hours postoperatively using a 5-point Likert scale (1 = very dissatisfied; 5 = very satisfied).[21] Finally, behavioral changes were evaluated three days after surgery via telephone interview using the Post-Hospitalization Behavior Questionnaire for Ambulatory Surgery.[22]

Adverse events were systematically documented using standardized forms throughout the perioperative period. Monitored complications included bradycardia, hypotension, laryngospasm, hypoxemia, postoperative nausea and vomiting, and nightmares. All outcome assessments were performed by a single investigator blinded to treatment allocation to ensure consistency and minimize bias.

Sample Size and Statistical Analysis

Based on Dixon's up-and-down methodology, dose-response studies typically require 24–26 participants to obtain six crossover points.[23] Following recent methodological guidance,[24] implemented a fixed prespecified sample size rather than a random stopping rule. We included 30 participants in each treatment group to enhance statistical reliability and account for potential withdrawals.

Statistical analyses followed a predetermined plan. Data normality was assessed using the Shapiro–Wilk test. Continuous data are presented as mean ± standard deviation for normally distributed variables and median (interquartile

range) for non-normally distributed variables. Categorical data are expressed as frequencies and percentages. We determined the sevoflurane MAC_{LMA} using Dixon's method and verified it through probit regression analysis.

Between-group comparisons employed appropriate parametric or non-parametric tests based on data distribution. One-way ANOVA with Bonferroni-adjusted post-hoc tests was applied to normally distributed variables, while the Kruskal–Wallis test, followed by Dunn's test with Bonferroni adjustment, was used for non-normally distributed data. Categorical outcomes, including emergence delirium, behavioral changes, and adverse events, were analyzed using chi-square or Fisher's exact tests as appropriate. All analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA), with statistical significance set at $p < 0.05$ (two-tailed).

Results

Between November 2023 and September 2024, we screened 98 children for study participation, with 90 meeting the eligibility criteria for randomization. Following protocol exclusions, the final analysis included 28 patients in the control group, 28 in the esketamine 0.5 mg/kg group, and 29 in the esketamine 1.0 mg/kg group (Figure 1). Demographic and baseline characteristics were similar across all groups (Table 1).

Our primary finding showed that intranasal esketamine premedication reduced the MAC_{LMA} of sevoflurane in a dose-dependent manner. These concentrations were 2.16% ± 0.18% (control, Figure 2A), 1.87% ± 0.17% (esketamine 0.5 mg/kg, Figure 2B), and 1.50% ± 0.19% (esketamine 1.0 mg/kg, Figure 2C), representing reductions of 13.4% and 30.6% from the control value, respectively. Probit regression analysis validated these findings, yielding comparable values of 2.06% (95% confidence interval [CI]: 1.85–2.26%) for control, 1.77% (95% CI: 1.60–1.95%) for esketamine 0.5 mg/kg, and 1.42% (95% CI: 1.27–1.59%) for esketamine 1.0 mg/kg groups (Figure 3).

The clinical benefits of esketamine extended beyond anesthetic reduction. Secondary outcomes revealed clear dose-dependent effects favoring the higher dose (Table 2). The 1.0 mg/kg group showed significantly improved cooperation during anesthesia induction compared to the control ($p < 0.001$), while the 0.5 mg/kg group showed no difference ($p = 0.756$). This dose-dependent pattern persisted through recovery: only the higher dose significantly reduced emergence delirium incidence (13.8% versus 46.4%, $p = 0.007$) and postoperative negative behavioral changes at day 3 (20.7%

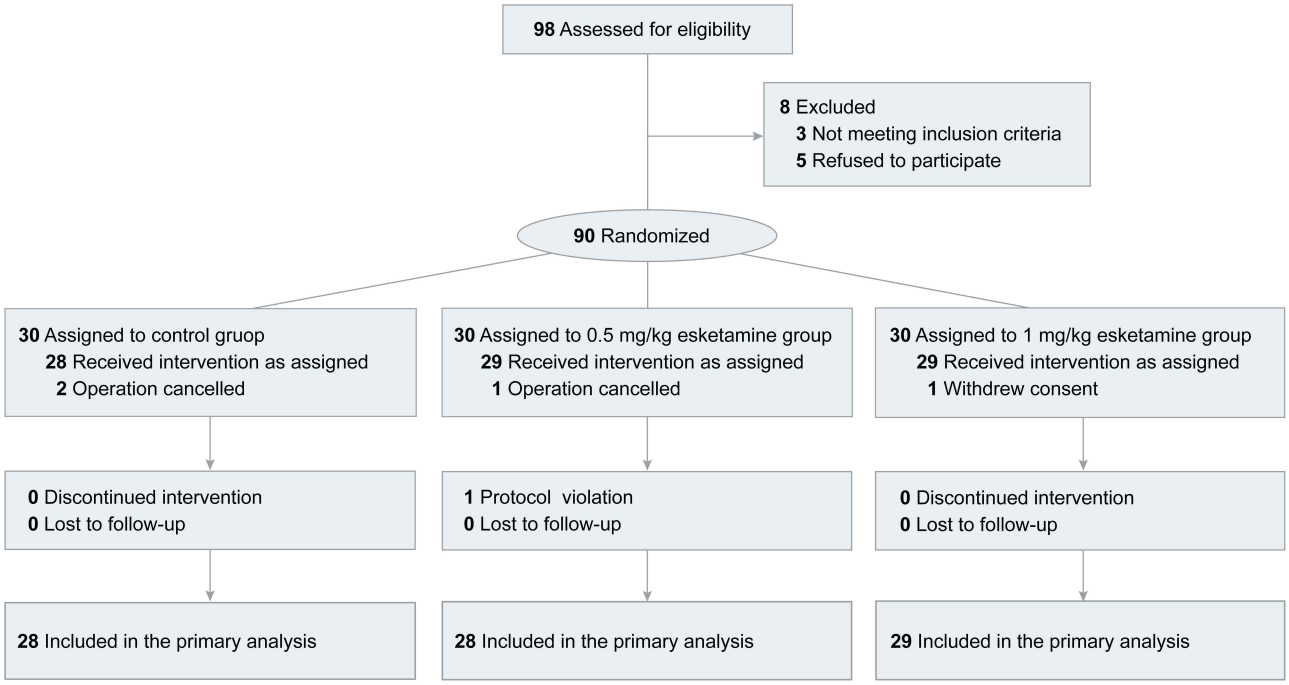


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

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Table 1 Baseline Characteristics

	Control (n=28)	0.5 mg/kg Esketamine (n=28)	1.0 mg/kg Esketamine (n=29)	p value
Age, month	47.5 (7.0)	49.8 (6.5)	48.0 (7.4)	0.292
Sex, n (%)				0.778
Female	10 (35.7)	11 (39.3)	13 (44.8)	
Male	18 (64.3)	17 (60.7)	16 (55.2)	
Weight, kg	15 [15–17]	17 [15–18]	16 [14–19]	0.335
Height, cm	103 [98–109]	104 [96–108]	102 [95–107]	0.447
BMI, kg/m^2	15.7 (1.7)	16.2 (1.8)	15.8 (1.6)	0.525
ASA physical status, n (%)				0.370
I	27 (96.4)	28 (100)	27 (93.1)	
II	1 (3.6)	0 (0)	2 (6.9)	
Body temperature, °C	36.6 [36.5–36.8]	36.7 [36.6–36.8]	36.8 [36.6–36.8]	0.201
Duration of surgery, min	23 [20–26]	22 [20–25]	22 [20–26]	0.560
Duration of anesthesia, min	40 [36–46]	39 [35–44]	39 [37–43]	0.571

Notes: Data are presented as mean (SD), median [IQR], or n (%).
Abbreviations: SD, standard deviation; IQR, interquartile range; ASA, American Society of Anesthesiologists; BMI, body mass index.

versus 53.6%, p = 0.010). Parents whose children received the higher dose reported significantly greater satisfaction (p = 0.022).

Importantly, these benefits came without compromising safety or prolonging recovery. Emergence times and PACU discharge readiness were similar across all treatment groups (p = 0.331 and p = 0.589, respectively). The incidence of adverse events (including bradycardia, hypotension, laryngospasm, hypoxemia, postoperative nausea and vomiting, and nightmares) showed no significant differences between groups, and no serious complications occurred throughout the study.

Discussion

Our findings demonstrate that intranasal esketamine premedication significantly reduces sevoflurane requirements during LMA insertion in pediatric patients in a dose-dependent manner. Both tested dosages (0.5 mg/kg and 1.0 mg/kg) produced clinically meaningful reductions compared to the control, with the higher dose providing approximately twice the effect. The 1.0 mg/kg dose conferred additional clinical benefits beyond anesthetic sparing, including enhanced induction cooperation, decreased emergence delirium, and reduced postoperative negative behavioral changes at day 3 postoperatively. Crucially, these advantages were achieved without extending recovery time or increasing adverse events.

These results build upon established research on NMDA in anesthesia practice. Chen et al showed that low-dose ketamine effectively reduces sevoflurane requirements for suppressing adrenergic responses during surgical procedures,[25] while Hamp et al[26] reported similar dose-dependent reductions with S-ketamine administration. Our findings advance this knowledge by demonstrating that the intranasal route achieves comparable anesthetic-sparing effects to intravenous administration while offering distinct advantages for pediatric patients, particularly avoiding injection-related distress. The observed dose-dependent relationship is consistent with known NMDA receptor antagonism pharmacological principles.

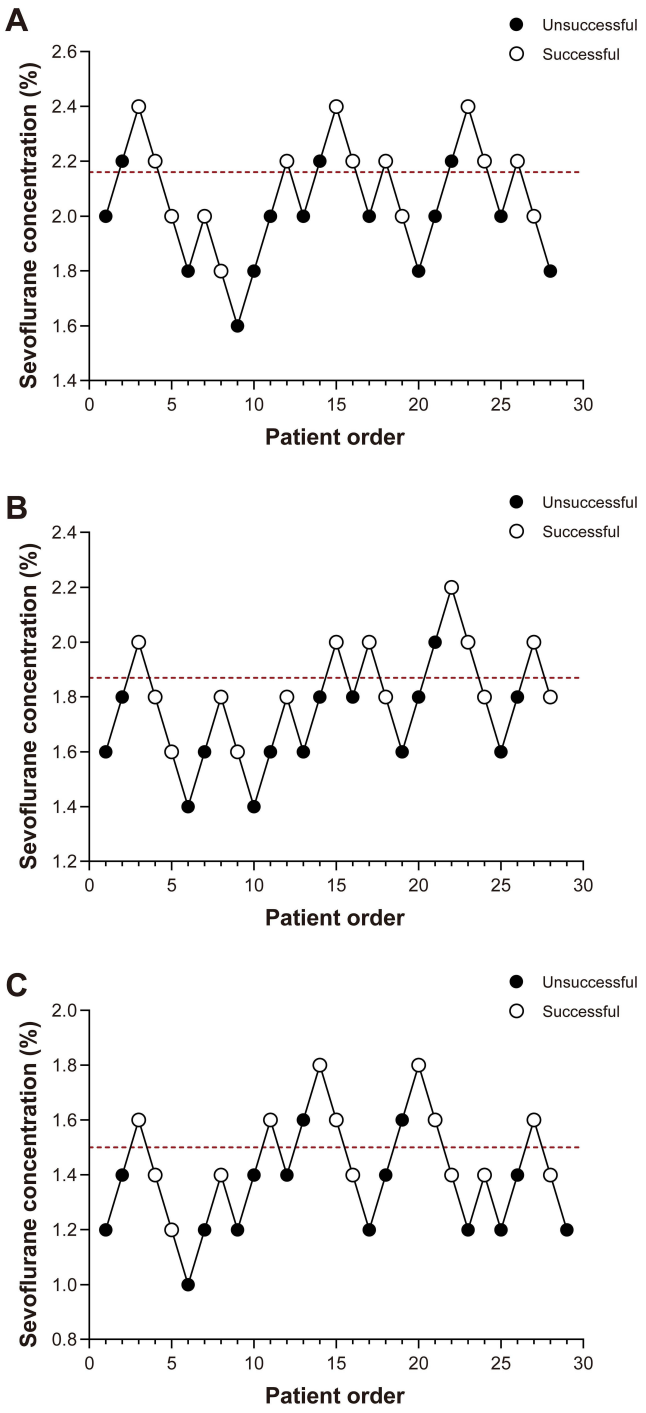

Figure 2 Individual responses to laryngeal mask airway insertion determined by Dixon's up-and-down method.
Notes: Sequential plots showing patient responses to laryngeal mask airway insertion across three treatment groups: (**A**) control, (**B**) esketamine 0.5 mg/kg, and (**C**) esketamine 1.0 mg/kg. Hollow circles represent successful insertions, while solid circles indicate unsuccessful insertions (characterized by movement, coughing, or bucking within one minute of placement). The horizontal dashed lines indicate the calculated minimum alveolar concentration of sevoflurane required for laryngeal mask airway insertion: 2.16% ± 0.18% (control group), 1.87% ± 0.17% (esketamine 0.5 mg/kg group), and 1.50% ± 0.19% (esketamine 1.0 mg/kg group). These values demonstrate a dose-dependent reduction in sevoflurane requirements with intranasal esketamine premedication.

Beyond anesthetic reduction, our study revealed important behavioral benefits. Intranasal esketamine at 1.0 mg/kg significantly reduced emergence delirium (13.8% versus 46.4%) and subsequent behavioral disturbances (20.7% versus 53.6%). These improvements align with Chen et al[27] who demonstrated that intravenous ketamine infusion (1 mg/kg bolus followed by 1 mg/kg/h infusion) reduced emergence delirium from 46% to 22% in children. Several mechanisms

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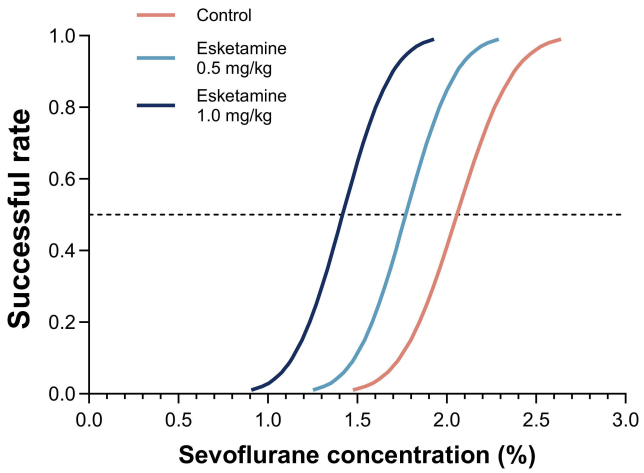

Figure 3 Probability curves for successful laryngeal mask airway insertion.
Notes: Probit regression analysis showing the probability of successful laryngeal mask airway insertion relative to sevoflurane concentration. Three treatment groups are represented: control (light red line), esketamine 0.5 mg/kg (medium blue line), and esketamine 1.0 mg/kg (dark blue line). The horizontal dashed line at 0.5 probability (50%) intersects with each curve at the minimum alveolar concentration value: 2.06% for control, 1.77% for esketamine 0.5 mg/kg, and 1.42% for esketamine 1.0 mg/kg. The progressive leftward shift of the curves with increasing esketamine dosage illustrates the dose-dependent reduction in sevoflurane requirements.

may explain these findings. Esketamine's anti-inflammatory properties could counteract surgery-induced neuroinflammation linked to postoperative behavioral changes.[28,29] Furthermore, esketamine's neuroprotective effects may reduce physiological stress responses to surgical and anesthetic stimuli, potentially protecting the developing brain from adverse changes.[30,31]

Table 2 Secondary Outcomes

	Control (n=28)	**0.5 mg/kg Esketamine (n=28)**	**1.0 mg/kg Esketamine (n=29)**	**p value**
Induction quality	3 [2–3]	3 [2–3]	4 [3–4]*	< 0.001
Peak PAED scale score	8.0 [6.0–11.0]	7.5 [5.0–10.0]	6.0 [4.0–8.0]*	< 0.001
Emergence Delirium, n (%)	13 (46.4)	9 (32.1)	4 (13.8)*	0.027
Emergence time, min	12.0 [10.0–13.0]	11.5 [10.0–13.5]	11.0 [10.0–13.0]	0.331
Length of PACU stay, min	23.5 [18.5–25.8]	20.5 [20.0–24.0]	21.0 [20.0–25.0]	0.589
Parental satisfaction	4 [2–4]	4 [3–4]	4 [4–5]*	0.010
PNBC at day 3, n (%)	15 (53.6)	9 (32.1)	6 (20.7)*	0.031
Adverse events, n (%)				
Bradycardia	3 (10.7)	1 (3.6)	1 (3.6)	0.415
Hypotension	1 (3.6)	0 (0)	0 (0)	0.357
Laryngospasm	1 (3.6)	1 (3.6)	0 (0)	0.588
Hypoxemia	1 (3.6)	1 (3.6)	1 (3.6)	> 0.99
PONV	3 (10.7)	5 (17.9)	4 (13.7)	0.743
Nightmare	9 (32.1)	11 (39.3)	8 (27.6)	0.639

Notes: Data are presented as mean (SD), median (IQR), or n (%). *Versus placebo, $p < 0.05$.
Abbreviations: IQR, interquartile range; PAED, Pediatric Anesthesia Emergence Delirium; PACU, postoperative anesthesia care unit; PNBC, postoperative negative behavioral changes; PONV, postoperative nausea and vomiting.

Several factors limit the interpretation of our results. The absence of pharmacokinetic measurements precluded detailed characterization of intranasal esketamine absorption profiles. Although we selected a 20-minute premedication interval based on published data indicating peak sedative effects at approximately 16 minutes,[11] this fixed timing may not have captured peak drug concentrations in all patients. Our single-center design involving a specific patient population undergoing eye muscle surgery may limit applicability to other pediatric surgical contexts. Testing only two doses provides incomplete information about the optimal dose across different age groups. Additionally, the varying sevoflurane concentrations required by the Dixon methodology could theoretically affect secondary outcomes, although the substantial separation between group values makes this unlikely. Finally, despite careful blinding protocols, esketamine's recognizable clinical effects may have compromised blinding in some cases.

Nevertheless, our study maintains high methodological standards. The randomized, double-blind, placebo-controlled design ensures robust internal validity. The Dixon sequential allocation method provided precise measurements of anesthetic requirement while protecting children from inappropriate depth. Our comprehensive pharmacodynamic and clinical outcomes assessment offers practitioners complete information about intranasal esketamine's effects. This approach demonstrates the quantitative reduction in sevoflurane requirements and the meaningful clinical improvements in children's perioperative experience.

Conclusion

Intranasal esketamine premedication significantly reduces sevoflurane requirements for LMA insertion in pediatric patients, with the 1.0 mg/kg dose achieving optimal results: 30.6% reduction in anesthetic requirements, improved induction cooperation, and decreased emergence agitation without prolonging recovery. These findings offer clinicians an evidence-based strategy to minimize volatile anesthetic exposure while maintaining airway safety. Although our single-center study involved a specific population undergoing strabismus surgery with one experienced operator, the results demonstrate clear clinical benefits. Future multicenter trials with diverse populations and practitioners should validate these findings and optimize dosing across age groups. Nevertheless, our data establish intranasal esketamine as a valuable tool for enhancing both safety and efficacy in pediatric anesthesia practice.

Data Sharing Statement

The corresponding author (Yanling Liao, Email: lyling0710@163.com) will make the deidentified participant data supporting this study's findings available upon reasonable request with a methodologically sound proposal. Data will become accessible six months after publication and remain available for three years thereafter. Requestors will be required to sign a data access agreement.

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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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Disclosure

The authors declare no conflicts of interest in this work.

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