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ARTICLE

Effect of the Preoperative Application of Esketamine on Stress Indicators in Paediatric Patients Undergoing Bronchoalveolar Lavage Under General Anaesthesia

Jizheng Zhang[1], Jiaming Zheng[2], Xiaohua Sun[1], Yi Li[1], Wanlu Ren[1,*]

[1]Department of Anesthesiology, Tianjin Hospital of Tianjin University, Tianjin, China
[2]West China School of Medicine, Sichuan University, Chengdu, Sichuan, China
*Correspondence: renwanlumazuike@163.com (Wanlu Ren)

Abstract

Aims/Background To explore the effect of the preoperative administration of esketamine on stress indices in paediatric patients undergoing bronchoalveolar lavage (BAL) under general anaesthesia.

Methods A retrospective cohort study was conducted to collect clinical data from children undergoing BAL under general anaesthesia in Tianjin Hospital of Tianjin University between February 2021 and January 2024. The patients were divided into two groups: the reference group (taking no preoperative medications) and the study group (receiving preoperative esketamine). The baseline variables of the two groups were balanced using the 1:1 nearest neighbour matching method of propensity score matching (PSM), and the outcome indicators of the matched cohorts were compared.

Results A total of 168 patients were included, including 86 in the reference group and 82 in the study group. After PSM, 46 cases in each group were successfully matched. Results showed that all postoperative stress indicators in the study group were significantly lower than those in the reference group ($p < 0.001$). The Paediatric Anaesthesia Emergence Delirium (PAED) scores and Face, Legs, Arms, Crying, Consolability (FLACC) scale scores of the children in the study group were significantly lower than those in the reference group ($p < 0.01$). There was no significant difference in the overall incidence of perioperative adverse reactions between the two groups ($p > 0.05$).

Conclusion The preoperative application of esketamine can reduce the stress response in paediatric patients undergoing BAL under general anaesthesia. This effect is beneficial for enhancing the outcome of surgical treatment.

Key words: preoperative period; esketamine; general anaesthesia; bronchoalveolar lavage; serologic tests

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Introduction

Bronchoalveolar lavage (BAL) is often used in clinical practice for the treatment and diagnosis of lung diseases (Post et al, 2024). Bronchoalveolar lavage fluid (BALF), enriched with a wide range of bioactive substances and cellular components, is a potential medium for liquid biopsy, containing biological information about key features of tumours and providing an auxiliary diagnostic tool to lung biopsy (Zhang et al, 2023). One study has reported administration of BAL in an elderly patient with Mendelson's syndrome undergoing orthopaedic surgery under general anaesthesia for an intertrochanteric fracture of the femur (Mishra et al,

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2025). Whole-lung lavage has long been a standard treatment option for pulmonary alveolar proteinosis (Gao et al, 2020). However, this procedure requires one-lung ventilation performed under general anaesthesia. It has found that general anaesthesia increases the incidence of postoperative cognitive dysfunction in patients (Tang et al, 2022). Moreover, the use of this anaesthetic regimen can lead to perioperative stress in patients due to anaesthetic drugs, surgical stimuli and pneumoperitoneum, ultimately leading to poor prognosis and suboptimal recovery.

The preoperative nasal spray esketamine has been reported to alleviate preoperative separation anxiety and reduce the risk of agitation in paediatric patients receiving strabismus surgery (Liu et al, 2022). Moreover, intravenous low-dose esketamine infusion combined with spinal anaesthesia has been found to reduce the incidence of post-cesarean section hypotension remarkably in women with preoperative anxiety, without causing considerable adverse effects on the foetus (Qi et al, 2024). On the basis of the above literature, we hypothesized that the preoperative use of esketamine may have a good anaesthetic effect in paediatric patients undergoing BAL under general anaesthesia. To the best of our knowledge, this is the first study attempting at investigating in this direction, underscoring the novelty and clinical significance in providing an additional basis for the selection of subsequent anaesthesia regimens.

Methods

General Information

Children undergoing BAL treatment in Tianjin Hospital of Tianjin University from February 2021 to January 2024 were selected as the study subjects. This study was approved by the ethics committee of Tianjin Hospital of Tianjin University (approval number: 2022003). Given that the study involved human beings, the study protocol was designed in accordance with the Declaration of Helsinki of the World Medical Association (2025). Informed consent was obtained from the legal guardians of the children after having been briefed and explained to about the purpose and significance of the study.

Inclusion and Exclusion Criteria

Inclusion criteria: (i) children had undergone BAL under general anaesthesia; (ii) children meeting American Society of Anaesthesiologists classes I–II; (iii) children aged 4–12 years old.

Exclusion criteria: (i) children with allergy to esketamine; (ii) children with cognitive impairment or inability to communicate; (iii) children with history of drug dependence; (iv) children with severe cardiac or pulmonary impairment, such as heart failure; (v) children with untreated active tuberculosis; (vi) children with incomplete clinical information.

Propensity Score Matching

The 1:1 nearest neighbour matching method of propensity score matching (PSM) was used. Matching covariates included age, gender, body mass index (BMI), respiratory rate, heart rate, white blood cell (WBC) count, procalcitonin (PCT), D-dimer,

disease type, and place of residence, with the caliper value set to 0.25. After PSM, 46 pairs of children were successfully matched, and the process is illustrated in Fig. 1.

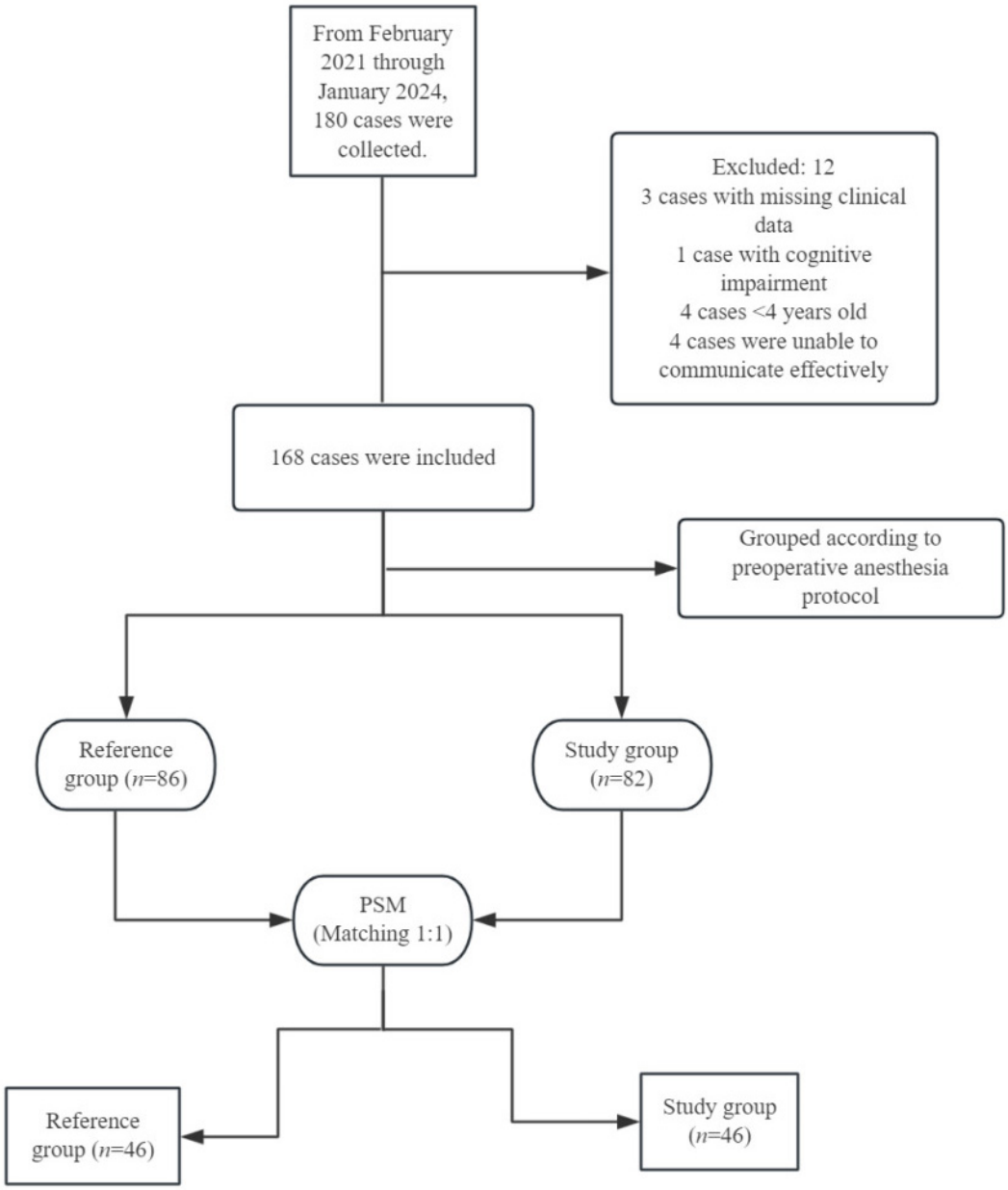

Fig. 1. Flowchart depicting participant selection and grouping. Abbreviation: PSM, propensity score matching.

Surgical Procedure

Preoperative Preparation

Inhaled corticosteroids and/or short-acting β2-agonists and lidocaine nebulised inhalation were given preoperatively to prevent the occurrence of intraoperative airway spasms. The patients were instructed to follow a defined fasting schedule for food and drink preoperatively, as follows: soft drinks for 2 h, breastmilk for 4 h;

milk, formula and liquid digestible food for 6 h; and fatty solid food for 8 h. All patients receiving the BAL treatment abstained from food and water until the gag reflex was restored (2 h after surgery). Preoperative examination was performed as follows: chest X-ray or chest computed tomography (CT) examination was completed before the surgery to determine the lesion site accurately to improve the diagnosis rate, and coagulation function, platelet count and electrocardiography were conducted to exclude children with potential bleeding risk and a history of cardiac disease. Preoperative examination was completed before the surgery. The bronchoscope model for children with a history of cardiac disease was selected as follows: in paediatric BAL, bronchoscopes with a diameter $\leq$2.8 mm are suitable for newborns and infants, and those with diameters of 4.0–4.9 mm are suitable for all age groups above 1 year old. In the reference group, non-use of drugs. In the study group, intravenous 0.5 mg/kg esketamine (2 mL, 50 mg; Yangzijiang Pharmaceutical Group Co., Ltd., Taizhou, China) was used.

Surgical Operation

For children with diffuse lesions, the middle lobe of the right lung or the left upper lobe was preferred for lavage; for those with limited lesions, the segment or lobe with the most severe lesion was selected. The volume of lavage was adjusted in accordance with body weight. For children weighing $<$20 kg, the total volume of lavage fluid was 3 mL/kg and the collected fluid was divided into three equal portions; for those weighing $\geq$20 kg, the volume of lavage fluid was 20 mL each time, and the maximum volume of lavage fluid was 3 mL/kg. Wall-type negative pressure suction was used for the intraoperative suction, and the negative pressure was maintained at 100–200 mmHg and adjusted at appropriate times to prevent the collapse of the bronchial lumen during suction. Glucocorticosteroids (e.g., budesonide) and/or expectorants (e.g., ambroxol) can be used for lavage treatment in accordance with the patient's disease condition. The first lavage was used for microbiological culture and analyses, and the second and third lavages were used for cytological and solute analyses, including protein and inflammatory factor analyses. The specimens were examined for BALF microbiology, cytology and noncellular components and subjected to the galactomannan antigen test.

Observation Indicators

The baseline data of the children were collected and recorded. These data included age, sex, BMI, heart rate, WBC count, D-dimer, PCT and disease type, as well as place of residence.

The serological parameters of the two groups of children were collected preoperatively and postoperatively, and the serum levels of cortisol, epinephrine and 5-hydroxytryptamine were measured by using enzyme-linked immunosorbent assay.

The quality of the awakening from anaesthesia among the children in the two groups was evaluated 1 h after awakening by using the Paediatric Anaesthesia Emergence Delirium (PAED) score (Bong and Ng, 2009), which includes five dimensions: eye contact, environmental perception, conscious behaviour, agitation or

delirium and uncontrollable crying. Each item has a score of 0–4 points, and the maximum total score is 20 points, with a higher score indicating more severe agitation in the children.

The Face, Legs, Arms, Crying, Consolability (FLACC) pain scale (Merkel et al, 1997) was used to assess the degree of postoperative limb pain in the two groups of children. It includes five items, namely expression, limb movement, behaviour, crying, and consolability. Each item is rated on a scale of 0–2. The maximum total score is 0–10 points, with a higher score indicative of more severe pain.

The incidence of perioperative adverse events in the two groups of children was recorded and compared.

Quality Control

The following methods were used to control bias in the study protocol and data processing. The study subjects were screened in strict accordance with the inclusion and exclusion criteria. The completeness of the clinical data and objectivity and quantifiability of the observation indices were ensured. Controversial clinical data were jointly interpreted by at least two researchers after comprehensive evaluation. PSM was applied to match the study subjects to reduce the interference of confounding factors.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corporation, Armonk, NY, USA) was employed to calculate and analyze the data collected in this study. Continuous variables were first tested for normality by using the Shapiro-Wilk test. Data that did not conform to the normal distribution are expressed as median (M) and interquartile range (P_{25}, P_{75}), and comparisons between groups were analyzed using the Mann-Whitney U test. Expressed as count and percentage, categorical variables were analyzed using the chi-square test or Fisher's exact probability method. The $p < 0.05$ was considered statistically significant.

Results

Patient Baseline Information and PSM Matching

A total of 168 children, including 86 cases in the reference group and 82 cases in the study group, were enrolled in accordance with the inclusion and exclusion criteria. The baseline information was matched as a predictor variable in accordance with PSM. A total of 46 cases in each group were successfully matched, and no significant difference between the baseline data of the two groups was found after matching ($p > 0.05$), indicating comparability between the two groups. The results are depicted in detail in Table 1.

Clinical Outcome Analysis

Comparison of Stress Indicators Between the Two Groups of Children After Matching

The results revealed no significant difference in the preoperative stress indicators between the two groups of patients ($p > 0.05$), whereas all the postoperative

Table 1. Comparison of baseline information before and after PSM in the two groups.

Variable	Before PSM						After PSM					
	Total (n = 168)	Reference group (n = 86)	Study group (n = 82)	Statistic	p	SMD	Total (n = 92)	Reference group (n = 46)	Study group (n = 46)	Statistic	p	SMD
Age (years), M (Q_1, Q_3)	9.00 (6.00, 11.00)	8.00 (6.00, 10.00)	9.00 (7.00, 11.00)	Z = –2.089	0.037	0.333	9.00 (6.00, 10.00)	9.00 (6.00, 10.00)	9.00 (7.00, 10.00)	Z = –0.606	0.545	0.162
BMI (kg/m^2), M (Q_1, Q_3)	18.30 (16.80, 20.00)	18.40 (16.80, 20.00)	18.20 (16.80, 19.95)	Z = –0.078	0.938	0.010	18.25 (16.80, 20.00)	18.00 (16.80, 20.10)	18.30 (17.20, 19.80)	Z = –0.408	0.684	0.085
Respiratory rate (breaths/min), M (Q_1, Q_3)	23.00 (21.00, 25.00)	24.00 (21.00, 26.00)	22.00 (20.00, 25.00)	Z = –2.505	0.012	–0.420	22.50 (21.00, 25.00)	22.00 (21.00, 24.00)	23.00 (20.00, 25.00)	Z = –0.041	0.968	–0.030
Heart rate (beats/min), M (Q_1, Q_3)	99.00 (94.00, 104.00)	101.50 (96.00, 106.00)	98.00 (93.00, 102.00)	Z = –3.942	<0.001	–0.664	98.00 (94.00, 103.00)	97.00 (94.00, 103.00)	98.00 (93.00, 103.00)	Z = –0.623	0.533	–0.146
WBC count ($\times 10^9$/L), M (Q_1, Q_3)	10.75 (9.20, 12.30)	11.10 (9.33, 12.30)	10.50 (8.83, 12.1)	Z = –1.446	0.148	–0.220	11.20 (9.43, 12.30)	11.10 (9.30, 12.20)	11.20 (9.90, 12.60)	Z = –0.751	0.453	0.158
PCT (μg/L), M (Q_1, Q_3)	0.13 (0.08, 0.18)	0.13 (0.08, 0.19)	0.12 (0.08, 0.18)	Z = –0.769	0.442	–0.119	0.12 (0.09, 0.18)	0.12 (0.09 0.19)	0.12 (0.10, 0.18)	Z = –0.558	0.577	–0.138
D-dimer (μg/mL), M (Q_1, Q_3)	1.14 (0.87, 1.49)	1.23 (0.93, 1.58)	1.02 (0.75, 1.39)	Z = –3.123	0.002	–0.514	1.12 (0.86, 1.47)	1.08 (0.88, 1.36)	1.17 (0.82 1.48)	Z = –0.323	0.747	0.062
Sex, n (%)				χ^2 = 4.598	0.032					χ^2 = 0.043	0.835	
Male	90 (53.57)	53 (61.63)	37 (45.12)			–0.332	45 (48.91)	23 (50.00)	22 (47.83)			–0.044
Female	78 (46.43)	33 (38.37)	45 (54.88)			0.332	47 (51.09)	23 (50.00)	24 (52.17)			0.044
Type of disease, n (%)				χ^2 = 9.618	0.022					χ^2 = 0.000	1.000	
Lower respiratory tract	87 (51.79)	54 (62.79)	33 (40.24)			–0.460	46 (50.00)	23 (50.00)	23 (50.00)			–0.000
Immunodeficiency pneumonitis	33 (19.64)	14 (16.28)	19 (23.17)			0.163	18 (19.57)	9 (19.57)	9 (19.57)			0.000
Others	23 (13.69)	7 (8.14)	16 (19.51)			0.287	10 (10.87)	5 (10.87)	5 (10.87)			0.000
Lower respiratory tract foreign body	25 (14.88)	11 (12.79)	14 (17.07)			0.114	18 (19.57)	9 (19.57)	9 (19.57)			0.000
Current address, n (%)				χ^2 = 6.856	0.009					χ^2 = 0.179	0.672	
Municipalities	64 (38.1)	41 (47.67)	23 (28.05)			–0.437	38 (41.30)	20 (43.48)	18 (39.13)			–0.089
Rural area	104 (61.9)	45 (52.33)	59 (71.95)			0.437	54 (58.70)	26 (56.52)	28 (60.87)			0.089

Note: The Q1 means “lower quartile”, and Q3 means “upper quartile”. Abbreviations: BMI, body mass index; PCT, procalcitonin; PSM, propensity score matching; WBC, white blood cell; SMD, standardized mean difference; M, median.

Table 2. Comparison of the stress indicators between the two groups of children after matching.

Groups	Cortisol (nmol/L)		5-HT (μmol/L)		Epinephrine (pg/mL)	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Study group	325.00 (295.98, 411.63)	643.95 (583.35, 710.48)	1.23 (0.86, 1.54)	3.39 (2.90, 3.75)	203.50 (119.75, 263.50)	695.50 (594.25, 775.50)
Reference group	338.30 (304.93, 435.35)	749.65 (658.38 ± 823.18)	0.95 (0.69, 1.71)	4.13 (3.73, 4.63)	157.50 (106.50, 212.25)	767.00 (692.50, 873.50)
z	−0.094	−4.654	−0.601	−5.748	−1.285	−3.584
p	0.925	<0.001	0.548	<0.001	0.199	<0.001

Notes: Data are expressed as M (P_{25}, P_{75}). Abbreviation: 5-HT, 5-hydroxytryptamine.

stress indicators in the study group were significantly lower than those in the reference group ($p < 0.001$), as depicted in Table 2.

Comparison of the Quality of Awakening From Anaesthesia and Pain Level Between the Two Groups of Children After Matching

The results in Table 3 showed that the PAED scores and FLACC scores of the children in the study group were significantly lower than those in the reference group ($p < 0.01$).

Comparison of the Occurrence of Perioperative Adverse Reactions Between the Two Groups After Matching

Our analysis also revealed no significant difference in the total incidence of perioperative adverse events between the two groups ($p > 0.05$), as depicted in Table 4.

Discussion

Escitalopram is the active enantiomer of the ketamine antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and is often used as a dissociative hallucinogen in inducing general anaesthesia (Li et al, 2025). As the *S*-enantiomer of ketamine, this drug has been shown to have two-fold greater analgesic potency and a lower incidence of adverse events than racemic ketamine. A randomized controlled trial by Huan et al (2025) suggests that the intraoperative application of esketamine reduces opioid consumption after gynecological laparoscopic surgery without increasing the risk of adverse events.

General anaesthesia administered through tracheal intubation induces a state of unconsciousness, analgesia and muscle relaxation, leaving the patient amenable to invasive procedures (Igarashi, 2024). However, some children may experience respiratory depression during tracheal intubation for general anaesthesia due to the distinctiveness of paediatric airways, as compared to the adults', such as flat tongues, short necks and vocal folds with a U-shaped and high position, all of which increase the difficulty of tracheal intubation (Schatzberg, 2021). Compared with conventional opioids, which directly inhibit the respiratory center, esketamine has a con-

Table 3. Comparison of the quality of awakening from anaesthesia and pain level between the two groups of children after matching.

Groups	PAED score	FLACC score
Study group (n = 46)	7.00 (5.00, 8.00)	4.00 (3.00, 5.00)
Reference group (n = 46)	10.00 (8.00, 11.25)	5.00 (4.00, 5.00)
z	–6.350	–4.577
p	<0.001	<0.001

Notes: Data are score points expressed as M (P_{25}, P_{75}). Abbreviations: PAED, Paediatric Anaesthesia Emergence Delirium; FLACC, Face, Legs, Arms, Crying and Consolability.

Table 4. Comparison of the occurrence of perioperative adverse reactions between the two groups after matching.

Groups	Nausea and vomiting	Delayed awakening	Postoperative mania	Total incidence
Study group (n = 46)	2 (4.35)	1 (2.17)	1 (2.17)	8.70% (4/46)
Reference group (n = 46)	3 (6.52)	2 (4.35)	2 (4.35)	15.22% (7/46)
χ^2				0.929
p				0.335

Note: Data are expressed as n (%).

siderably milder inhibitory effect on the respiratory center (Lu et al, 2022). As has been reported (Zhao et al, 2025), esketamine, a novel anaesthetic analgesic without a remarkable effect on respiratory function, reduced the incidence of intraoperative adverse effects in patients undergoing painless gastroenteroscopy when combined with remazolam. A report in the literature on geriatric orthopaedic surgery also found that the use of low-dose eketamine in the induction of anaesthesia in elderly patients undergoing knee arthroplasty resulted in the improved maintenance of haemodynamic stability, which was beneficial for postoperative recovery (Li et al, 2022). Compared with thoracoscopic lobectomy (Wang et al, 2025), esketamine in the present study showed significant stress-modulating effects at a lower dose, which may be related to the shorter duration of BAL operations and the relative limitation of mechanical stimulation (Cornelissen et al, 2021; Naamany et al, 2025). However, compared with the nebulized inhalation administration protocol during one-lung ventilation procedures (Chen et al, 2023), the intravenous route of administration in the present study may be more suitable for BAL operations requiring frequent airway suctioning, as it may provide more consistent systemic analgesia and sedation. This study was conducted in a group of children with lower respiratory tract infections and immunodeficiency pneumonitis with unique pathophysiologic characteristics. Unlike children undergoing conventional surgery, these patients often have airway hyperresponsiveness and reduced lung compliance, which may result in a more intense stress response to surgical stimuli. The anti-inflammatory properties of esketamine in these patients may be related to its inhibition of NMDA receptor-mediated neuroendocrine activation, which partly explains why the decrease in stress indicators in the present study was greater than in other surgery-

oriented studies. In terms of dosing regimen, the intravenous injection (0.5 mg/kg) in the present study may have provided a more stable drug concentration compared to the nasal spray regimen (Seshadri et al, 2024), which is essential for suppressing persistent irritation during BAL operations. Notably, the pharmacokinetic differences between children and adults suggest the need to optimize dosing regimens for children of different ages and to select the appropriate type of surgery, rather than simply applying the standard doses used by adult patients. In the present study, we found that the preoperative application of esketamine reduced the level of stress indicators in children. This effect was conducive to maintaining the stability of intraoperative physiological indicators, protecting tracheal function and reducing the risk of postoperative complications. This result shares similarities with the findings of Jia et al (2025), thus confirming that esketamine is beneficial in reducing perioperative stress indicators in patients. The presumed reason may be that the drug is a noncompetitive antagonist of NMDA receptors and inhibits central sensitization and pain signaling by blocking glutamatergic neurotransmission. This action reduces the transmission of injurious stimuli induced by surgical trauma to the center, thereby reducing the stress response.

In addition, our study found that the preoperative application of esketamine demonstrated a remarkable effect in improving the quality of awakening from anaesthesia and pain levels in children likely because esketamine, through its pharmacological effects, helps regulate the central nervous system and promotes the smooth awakening of the patient after surgery. Compared with those who did not use the drug, patients treated with esketamine showed faster recovery of consciousness, less agitation, and smoother physiological responses preoperatively, which directly enhanced the quality of their awakening from anaesthesia. This is probably attributed to the fact that the drug promotes rapid awakening from anaesthesia by activating glutamatergic neurons in the paraventricular nucleus of the thalamus, and accelerates the return of consciousness, possibly by enhancing synaptic transmission between cortex and thalamus (Han et al, 2023). In addition, esketamine has a good analgesic effect, which can effectively reduce the discomfort caused by the inflammatory reaction of the tissues possibly triggered by surgical manipulation and thus ameliorate postoperative pain, as shown by Ding and Yue (2024). However, our present study did not find any significant difference between the two groups in terms of the incidence of perioperative complications. This result may be related to factors, such as the small size of the sample, type and complexity of complications, and method of monitoring and recording.

Although this study has made some research progress, several limitations should be acknowledged. For example, it is a clinical retrospective study, which may result in information bias. In addition, its research questions focusing on the existing variables make exploring new hypotheses difficult. Furthermore, our study only included paediatric patients from a single center. Such an approach may result in a lack of sample diversity and make generalizing its results to other populations or healthcare environments challenging. Moreover, small sample size renders this study unable to detect actual effects, resulting in the erroneous acceptance of null hypotheses. Cortisol and epinephrine secretion has a significant circadian rhythm,

with levels varying with time-of-day fluctuations. Therefore, standardization of blood collection times is critical for data accuracy in postoperative studies. However, postoperative blood collection times are often difficult to fully standardize due to the fact that surgery times are limited by clinical realities, e.g., operating room scheduling, emergency table insertion, etc., which is a common challenge in this type of study. To reduce this interference, subsequent studies could optimize the protocol in two ways: first, limiting the time period of surgery, such as performing surgery only in the morning, to control the rhythmic effects of hormone secretion. The second is to increase the postoperative sampling time points, e.g., fixing the blood collection at 2, 6, and 24 h postoperatively, and correcting for temporal differences through multipoint data. These improvements help to obtain more objective and accurate hormone level results. Therefore, prospective, multicenter, large-sample studies should be conducted in future investigations, in considering trade-offs between scientific rigor and clinical utility, particularly in resource-constrained settings.

Conclusion

This study provides compelling evidence for optimizing perioperative management involving the use of esketamine in children undergoing BAL under general anaesthesia. This regimen was found to be effective in decreasing stress indicators, improving the quality of awakening from anaesthesia and alleviating postoperative pain.

Key Points

- Escitalopram is effective in suppressing the stress response induced by general anaesthesia and surgical operations.
- Preoperative application of esketamine helps to improve the quality of the awakening from anesthesia and reduce the incidence of agitation in children.
- Preoperative use of esketamine is effective in relieving pain in children's extremities.
- Preoperative application of esketamine does not increase the incidence of adverse effects in children, showing a good safety profile.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

JZZ and WLR designed the research study. YL and WLR performed the research. JMZ and XHS analyzed the data. JZZ drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read

and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Tianjin Hospital of Tianjin University (approval number: 2022003). Given that the study subjects involved human beings, the study protocol was designed in accordance with the Declaration of Helsinki, and the enrolled patients signed a written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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