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Low-dose Esketamine combined with Propofol in microscopic pediatric strabismus surgery: a randomized controlled study

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Abstract

Objective To observe the effect of low-dose esketamine combined with propofol in pediatric strabismus surgery.

Methods A total of 84 children aged 3–15 years, regardless of gender, with a BMI of 13–26 kg/m^2, ASA grade I or II, were selected for elective microscopic strabismus surgery and divided into two groups based on the randomized numerical table: esketamine group (group E) and propofol group (group C), with 42 patients in each group. Group E was pre-injected with esketamine 0.2 mg/kg, and propofol 2.5 mg/kg was slowly injected after one minute. Group C was pre-treated with an equal volume of saline, and propofol 2.5 mg/kg was administered slowly after one minute. The occurrence of propofol injection pain was assessed using the Verbal Rating Scale (VRS). HR and MAP were recorded in the two groups at 5 min before induction, after induction, at the start of the procedure, and at the end of the procedure. operative time, extubation time and post-anesthesia care unit (PACU) stay were recorded. The Pain Behaviour Scale for Children (Face, Legs, Activity, Cry, Consolability, FLACC) scores at the time of discharge from the PACU and at 1day, 3days and 7days postoperatively were recorded. perioperative tachycardia, emergence agitation, oculocardiac reflex, extubation cough and other adverse reactions were also recorded.

Results Compared with Group C, Group E exhibited significantly lower rates of propofol injection pain(cases (%), 87.5% VS 56.1%, $P=0.002$), and moderate-to-severe pain during induction(75.0% VS 24.4%, $P<0.001$), reduced FLACC scores at PACU discharge(median and interquartile spacing [M(IQR)], 3.50(4) VS 3.00(2), $P=0.039$) and 1 day postoperatively(M(IQR), 5.00(3) VS 3.00(2), $P<0.001$), and decreased incidences of adverse events including emergence agitation(32.5% VS 12.2%, $P=0.028$), oculocardiac reflex(35.0% VS 14.6%, $P=0.034$), and extubation cough(25.0% VS 7.3%, $P=0.030$). However, no statistically significant differences were observed between the two groups in operative duration, extubation time, PACU stay duration, FLACC scores at 3 and 7 days postoperatively, or heart rate and mean arterial pressure at any measured time point.

Conclusion General anesthesia with low-dose esketamine combined with propofol for pediatric strabismus correction surgery effectively alleviates propofol injection pain, reduces FLACC scores at PACU discharge and 1 day

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postoperatively, and decreases the incidence of adverse reactions such as emergence agitation, oculocardiac reflex, and extubation cough, demonstrating its safety for use in this procedure.

Trial registration This study was approved by the Scientific Research and Clinical Trials Ethics Committee of The First Affiliated Hospital of Zhengzhou University (Approval No. 2023-KY-1509), registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2400092266, registration date on 11/13/2024).

Keywords Esketamine, Propofol, Pediatric strabismus surgery, Propofol injection pain, Emergence agitation

Introduction

Strabismus, a prevalent eye ailment, impacts not just the functionality of the eye but also influences the patient's facial features and social interactions. Among eye surgeries, strabismus surgery ranks as the most frequently conducted on children. Owing to the surgery's sensitive characteristics, maintaining a constant eye position is necessary. Most children are unable to cooperate with the operation, so strabismus surgery must be performed under general anesthetic. Surgical intervention for strabismus remains the cornerstone in the clinical management of this condition in children.Adjusting the length and position of the extraocular muscles under the microscope improves their coordination and restores normal visual function [1], which has a positive impact on the quality of life and psychosocial functioning of the child and their parents [2]. Microscopic pediatric strabismus surgery is a short procedure, but the surgical stimulus is strong, and effective sedation and analgesia are required during the operation.

Esketamine, a right-handed variant of ketamine [3], demonstrates promising potential in pediatric anesthesia due to its rapid onset of action, short duration of maintenance, sympathomimetic effects and fewer adverse effects. Propofol, as a commonly used intravenous anaesthetic, is widely used in the clinic because of its rapid onset of action, controllability and minimal side effects, but its main adverse reaction is injection pain, with an incidence rate of 28–90% [4–5], which is a thorny problem in pediatric patients, the injection pain of propofol can cause children to cry, feel irritated, make noticeable body movements and even leave psychological shadowing.

Pediatric strabismus surgery demands anesthetic regimens that balance intraoperative hemodynamic stability with rapid postoperative recovery. However, conventional protocols relying solely on propofol are limited by its lack of intrinsic analgesia, propofol-induced injection pain, and dose-dependent hemodynamic instability. While ketamine has historically been used to mitigate these challenges, its racemic form is constrained by psychomimetic side effects (e.g., hallucinations, emergence delirium) and potential intraocular pressure (IOP) elevation, particularly in ocular procedures. While esketamine's safety in adults is well-established, pediatric-specific evidence for low-dose protocols remains limited. This gap is particularly consequential given the rising demand for ambulatory strabismus surgery, which necessitates rapid recovery without compromising surgical precision or pediatric neurobehavioral outcomes. Based on the pharmacodynamic synergy between esketamine and propofol, we hypothesized that, compared with propofol alone, the addition of low-dose esketamine to propofol induction would reduce propofol injection pain and early postoperative pain, improve hemodynamic stability, and decrease the occurrence of perioperative adverse events (such as oculocardiac reflex, coughing during extubation, and postoperative agitation) in pediatric patients undergoing strabismus surgery. In order to improve the comfort of anaesthesia and promote medical comfort, this study aims to observe the application effect of low-dose esketamine combined with propofol in microscopic pediatric strabismus surgery.

Methods

General information

This study was a randomized controlled trial and was approved by the Scientific Research and Clinical Trials Ethics Committee of The First Affiliated Hospital of Zhengzhou University (Approval No. 2023-KY-1509), registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2400092266), and written informed consent was obtained from all pediatric patients and their legal guardians. The trial enrolled patients who were aged 3–15 years, with no gender restrictions, BMI 13–26 kg/m^2, and ASA classification of I or II, who were scheduled to undergo microscopic strabismus surgery from November 15, 2024 to January 31, 2025 in the First Affiliated Hospital of Zhengzhou Univesity in China. Exclusion criteria included: preoperative crying or distress before propofol administration, patients with preexisting elevated intraocular pressure or increased intracranial tension, severe cardiopulmonary comorbidities, psychiatric disorders, non-primary strabismus correction surgery, and hypersensitivity to esketamine or propofol. Elimination criteria comprised intraoperative conversion to a different surgical procedure, voluntary withdrawal during the study period, or postoperative loss to follow-up. The study was initially registered as a 3-arm trial (ChiCTR2400092266) but was streamlined to 2 groups

during implementation to prioritize esketamine's dose-response evaluation. Participants were randomized using a random number table method into either the esketamine group (Group E) or the propofol group (Group C).

Patients were randomised into two groups using a random number table method. Sequentially numbered, opaque, sealed envelopes containing group assignments were prepared by an independent statistician and stored in the operating theater. Intraoperatively, a designated anesthesiologist (not participating in recruitment, data collection, or analysis) opened the envelope only after confirming patient eligibility and obtaining written informed consent, thereby ensuring allocation concealment. Study drugs were prepared in identical syringes labeled with patient ID numbers to ensure blinding of patients, surgeons, and outcome assessors. The trained professionals who collected the data were not involved in anaesthesia delivery or aware of group allocations.

Anaesthesia methods

All children were routinely fasted for 8 h and were instructed to abstain from drinking for 2 h before surgery. Upon the children entering the room, the medical staff established peripheral venous access, regularly monitored HR, NIBP, SpO_2, ECG, and $P_{ET}CO_2$ levels, and maintained thermal protection between 36 and 37 °C. Initially, Group E received an intravenous injection of 0.2 mg/kg esketamine (Jiangsu Hengrui Medicine Co, Ltd, State Pharmaceutical Approval H20193336), succeeded by a gradual 2.5 mg/kg injection of propofol (Jiangsu Enhua Pharmaceutical Co, Ltd, State Pharmaceutical Approval H20123138) after one minute. Group C received a saline injection of the same volume, followed by a gradual 2.5 mg/kg injection of propofol after one minute. Subsequently, each patient received alfentanil 50 μg/kg and rocuronium bromide 0.6 mg/kg in sequence,. After induction of anaesthesia, when the patient's muscles were sufficiently relaxed, a suitable laryngeal mask was installed, and a ventilator was set up for mechanical ventilation with a tidal volume between 6 and 8 ml/kg, an oxygen concentration of 40%, an oxygen flow rate of 2.0 L/min and an inhalation/exhalation ratio of 1:1.5, and the respiratory rate was adjusted to maintain a $P_{ET}CO_2$ between 35 and 45 mmHg during the operation (1 mmHg = 0.133 kPa). Anaesthesia was maintained by sedation-aspiration complex anaesthesia with 3-5% sevoflurane by inhalation and target-controlled infusion of propofol and remifentanil. The administration of Sevoflurane ceased five minutes prior to the surgery's conclusion, and flurbiprofenate 1 mg/kg and Ondansetron 0.1 mg/kg were given. At the end of the surgery, the child was transferred to the PACU equipped with a resuscitation tube, and the laryngeal mask was removed when the child's spontaneous breathing was fully restored. If the child became agitated during the recovery period, propofol 1 mg/kg was given to assist with sedation.

Observation indicators

Primary outcome measure: Verbal Rating Scale (VRS) was used to assess the occurrence of propofol injection pain (PIP) in children (score 0: no pain, no response to questioning; score 1: mild pain, pain indicated by questioning but no motor response; score 2: moderate pain, pain indicated by questioning and motor response; score 3: severe pain, characterized by the patient's strong complaints of pain and accompanied by arm withdrawal, tearing and other behaviours).

Secondary outcome measures: We recorded the HR and MAP of children in the two groups 5 min before induction, after induction, at the beginning of the operation, at the end of the operation. Also, we recorded the duration of the operation, the time of extubation, and the time of stay in the Post-Anesthetic Care Unit (PACU). Moreover, we recorded the Children's Pain Behavioral Scale scores (Face, Legs, Activity, Cry, Consolability, FLACC) at the time of discharge from the PACU, and at 1 day, 3 days, and 7 days postoperatively [6], as well as the occurrence of perioperative adverse reactions such as perioperative tachycardia, emergence agitation, oculocardiac reflex (OCR, which was recorded if the heart rate decreased by 20% or more from baseline during the procedure), and extubation cough.

Statistical analysis

PASS 2021 software was used for sample size estimation. Referring to previous studies [7], the incidence of propofol-induced pain in children treated with general anaesthesia for strabismus surgery can be up to 85%. Based on pre - experimentation results, we anticipated that the incidence of propofol - induced pain (PIP) in the low - dose esketamine combined with propofol group would decrease by at least 30% (effect size: from 85 to 55%). We set $\alpha = 0.05$ (two - tailed) for a significance level, $1 - \beta = 0.8$ for power, and accounted for a 20% dropout rate. Ultimately, 84 patients were included in the study, 42 patients in each group.

SPSS 25.0 software was used for data analysis. Measurement information was expressed as mean ± standard deviation ($\bar{x} \pm s$), and an independent samples t-test was used for comparison between groups. Otherwise, it was expressed as median and interquartile spacing [M(IQR)], and the Mann-Whitney test was used for comparison between groups; counting information was expressed as cases (%), and group comparison was used by the χ^2 test. $P < 0.05$ was considered a statistically significant difference.

Table 1 Comparison of general information of the two groups of patients

Group	Number of cases(*n*)	Sex (male/female)	Age (years)	BMI(kg/m^2)	ASA(I/II cases)	operation duration(min)	extubation time (min)	PACU stay time (min)
Group E	41	20/21	6.32 ± 1.665	15.91(1.66)	38/3	17.00(7)	18.00(7)	33.00(6)
Group C	40	21/19	5.70 ± 1.772	15.95(2.52)	35/5	15.00(11)	21.00(10)	34.00(10)
Statistical Measure		0.112	1.616	0.312	0.167	0.441	0.541	1.193
P-value		0.738	0.110	0.755	0.682	0.660	0.589	0.233

Values are expressed as mean ± SD or number of patients; BMI: Body mass index, ASA: American Society of Anesthesiologists physical status; PACU: Post-anesthesia Care Unit

Table 2 Comparison of the occurrence of PIP in the two groups[cases (%)]

Group		VRS			Total patients experienced pain
	Number of cases(*n*)	0	1	2–3	
Group E	41	18(43.9)	13(31.7)	10(24.4)	23(56.1)
Group C	40	5(12.5)	5(12.5)	30(75.0)	35(87.5)
Statistical Measure		9.820	4.322	20.747	9.820
P-value		0.002	0.038	<0.001	0.002

Values are expressed as numbers (percentages); VRS: Verbal Rating Scale

Table 3 Comparison of the occurrence of FLACC in the two groups

Group	Number of cases(*n*)	PACU discharge	Postoperative day 1	Postoperative day 3	Postoperative day 7
Group E	41	3.00(2)	3.00(2)	1.00(2)[a]	1.00(1)[a]
Group C	40	3.50(4)	5.00(3)[a]	1.00(2)[a]	1.00(1)[a]
Statistical Measure		4.265	29.103	0.936	0.343
P-value		0.039	<0.001	0.333	0.903

Between-group effect: F = 20.768, $p < 0.001$; time effect: F = 187.694, $p < 0.001$; interaction effect: F = 22.713, $p < 0.001$

Note: Compared with PACU discharge, [a]$P < 0.05$

Results

Eighty-four patients were initially enrolled in this study, one patient in group E withdrew spontaneously, one patient in group C withdrew spontaneously, and one patient was lost to follow-up, and 81 patients were finally included in the analysis. There was no statistically significant difference between the two groups in terms of gender, age, BMI, ASA classification, duration of surgery, extubation time, and stay in the PACU (Table 1).

The incidence of PIP was 56.1% and 87.5% in groups E and C, respectively. The incidence of PIP($P = 0.002$) and moderate-to-severe pain ($P<0.001$) at the time of induction were significantly lower in group E compared with group C (Table 2).

Compared with PACU discharge, both Group E and Group C demonstrated significantly lower FLACC scores at postoperative day 3 and day 7, whereas Group C exhibited a notable increase in FLACC scores at postoperative day 1. When compared to Group C, Group E showed significantly lower FLACC scores at PACU discharge($P = 0.039$)and postoperative day 1 ($P <0.001$), but no statistically significant differences were observed between the two groups at postoperative day 3 and day 7 (Table 3).

Compared with the 5 min before induction, HR and MAP were significantly lower in both groups after induction, at the beginning of surgery, and at the end of surgery; the differences in HR and MAP at different time points between the two groups were not statistically significant (Table 4).

Compared with group C, the incidence of emergence agitation($P = 0.028$), oculocardiac reflex ($P = 0.034$), and extubation cough ($P = 0.030$) was significantly lower in group E; the difference in the incidence of tachycardia between the two groups was not statistically significant (Table 5).

Discussion

Strabismus surgery requires stable head and eyeball. Since children can't cooperate with local anesthesia, general anesthesia is commonly used. Propofol is widely applied in pediatric intravenous general anesthesia for its rapid induction and controllability [8]. Esketamine has intrinsic analgesic, hypnotic, sedative, antihyperalgesia, and antidepressant effects [9–10], and its affinity for NMDA and μ receptors is twice that of ketamine, and half the dose of ketamine is required to achieve the same effect [11], minimizing dissociative side effects. Its

Table 4 Comparison of HR and MAP at different time points between the two groups ($\bar{x} \pm s$)

Parameter	Group	Number of cases(*n*)	5 min before induction	post-induction	beginning of surgery	End of Surgery
HR(bpm)	Group E	41	94.00(12)	85.00(18)[a]	75.00(17)[a]	74.00(9)[a]
	Group C	40	88.50(20)	80.00(15)[a]	80.00(20)[a]	78.00(16)[a]
MAP(mmHg)	Group E	41	82.00(13)	73.00(14)[a]	72.00(16)[a]	71.00(12)[a]
	Group C	40	78.00(13)	65.50(14)[a]	66.50(17)[a]	70.00(14)[a]

HR: heart rate; MAP: mean arterial pressure; bpm: beats per minute; MAP: between-group effect: F = 2.894, *P* = 0.089; time effect: F = 76.224, *P* < 0.001, interaction effect: F = 10.702, *P* = 0.013; HR: between-group effect: F = 0.018, *P* = 0.894; time effect: F = 155.603, *P* < 0.001, interaction effect: F = 14.755, *P* = 0.002

Note: Compared with the 5 min before induction, [a]*P* < 0.05

Table 5 Comparison of the occurrence of perioperative adverse reactions between the two groups [cases (%)]

Group	Number of cases(*n*)	Tachycardia	Emergence Agitation	Oculocardiac Reflex	extubation cough
Group E	41	3(7.3)	5(12.2)	6(14.6)	3(7.3)
Group C	40	6(15.0)	13(32.5)	14(35.0)	10(25.0)
Statistical Measure		0.557	4.830	4.516	4.699
P-value		0.455	0.028	0.034	0.030

enhanced μ-opioid receptor activity further supports hemodynamic stability and analgesia, making it particularly advantageous in children requiring rapid postoperative recovery. As per prior literature, the subanaesthetic dosage of esketamine is 0.15–0.25 mg/kg (ketamine: 0.3–0.5 mg/kg) [12]. Furthermore, esketamine has a faster rate of clearance in the body and a shorter wake-up time, and relatively fewer adverse effects. Hence, the combination of the two drugs is safe and effective [13], providing synergistic analgesia, rapid and smooth induction of anaesthesia, and maintenance of stable intraocular pressure [14].

The occurrence of PIP during intravenous propofol injection is mainly related to two aspects. One is the direct stimulation of the vascular endothelium by the free drug. The other is the release of inflammatory mediators such as bradykinin, which stimulates the injury receptors and nerve endings [7]. This burning-like pain along the vascular course often causes nervousness and fear and leaves the child with a painful memory. There are many schemes to alleviate propofol injection pain in the past, such as pretreatment with lidocaine combined with a tourniquet, ketamine, opioids, paracetamol, etc. Combining lidocaine is a common scheme. As a local anesthetic, it can bind to pain receptors in blood vessel walls, and block cellular voltage - gated sodium channels to exert anesthetic effects. Pretreatment injection can form a venous regional block or block the mediators. However, mixing into propofol may change the pharmacological properties and increase the risk of adverse reactions, particularly in pediatric doses requiring precise titration.

In this study, we found that the incidence of PIP and moderate-to-severe pain at the time of induction was significantly reduced in Group E. The incidence of PIP and its pain level were reduced by esketamine, which prevents the transmission of injurious messages by inhibiting the activity of NMDA receptors and exerts its anaesthetic and analgesic effects. This result is of great significance to the children because they have poor tolerance to pain. Reducing PIP not only improves the children's comfort and cooperation during the induction stage of anaesthesia but also reduces anxiety, crying, and other adverse emotions caused by pain, which helps to enter the anaesthesia state smoothly and creates favourable conditions for subsequent surgical operations.

The results of a meta-analysis showed that esketamine, when used as an adjuvant to general anaesthesia, can significantly exert analgesic effects and effectively reduce the degree of pain in the early postoperative period [15], which is consistent with the results of the present study. The FLACC scores of group E were notably lower than those of group C at the time of discharge from the PACU and at 1 d postoperatively, which may be attributed to the fact that esketamine can directly inhibit NMDA receptors and decelerate their separation, thereby producing a sustained blocking effect [16]. It can be converted to the less pharmacologically active norethindrone, which is less analgesic than esketamine but has a longer elimination half-life [17], and this makes it possible for its analgesic effect to persist into the early postoperative period. In addition, esketamine has a significant anti-inflammatory effect, which can reduce the release of inflammatory factors triggered by oxygen-free radicals, effectively alleviate the inflammatory response, and provide a favourable environment for patients to recover [18–19]. However, there was no significant difference in FLACC scores between the two groups of patients in this study at 3 days and 7 days postoperatively, which may be attributed to the shorter operative time and less traumatic surgery of microscopic pediatric strabismus surgery, resulting in lower pain levels at 3 days and 7 days postoperatively. Effective pain control in the early postoperative period may promote rapid postoperative recovery and reduce

pain-induced stress, thereby reducing the risk of cardiovascular and cerebrovascular complications.

There was no statistically significant difference in the comparison of HR and MAP between the two groups at any time point in this study. Esketamine has sympathomimetic excitatory effects, which can increase blood pressure and accelerate heart rate, counteracting the hypotension induced by propofol and mitigating the adverse effects on heart rate. The combination of these two effects, together with the body's compensatory mechanisms, allowed the children's circulatory systems to remain relatively stable during surgery [20], ensuring the perfusion of vital organs and reducing the surgical risks associated with hemodynamic fluctuations.

The incidence of emergence agitation(EA) in children is approximately 10–80% [21], which may be related to the physiological characteristics of children themselves, as well as the residual effects of anaesthetics, pain stimulation, etc. [22]. The risk of EA after ophthalmic surgery is higher than after other types of surgery [23], and pain has been found to be an independent risk factor for the development of EA, with a 1.3-fold increase in the risk of EA for every 1-point increase in postoperative pain [24]. In the present study, the prophylactic use of esketamine was effective in relieving the children's nervousness and anxiety and in controlling pain in the early postoperative period and therefore had a preventive effect on postoperative agitation during the waking period. Previous studies have shown that esketamine can reduce the incidence of arousal agitation in children [25–26], and the incidence of adverse reactions such as emergence agitation, oculocardiac reflex, and extubation cough in group E was significantly lower than that in group C in this study, which may be attributed to the fact that esketamine in combination with propofol can provide better pain control and smoother anaesthesia emergence, which reduces the incidence of emergence agitation, Meanwhile, esketamine has an anti-inflammatory and central nervous system protective effect [19], which reduces excitability during the wakefulness period. The oculocardiac reflex is a relatively common complication of strabismus surgery and its occurrence is related to the pulling of the extraocular muscles by the surgical procedure. Premedication with 0.15 mg/kg intravenous ketamine may reduce the incidence of the oculocardiac reflex [27]. Esketamine, the dextro isomer of ketamine, inhibits the afferent and efferent pathways of the oculocardiac reflex by regulating the balance of the autonomic nervous system, thereby reducing the incidence of the reflex [28]. Extubation cough is mainly related to airway irritation and incomplete activation of cough receptors during anaesthesia emergence. Esketamine can inhibit cough by broadly inhibiting NMDA receptors located in the trachea and lungs [29–30], and it can directly act on L-type voltage-dependent calcium channels of airway smooth muscle to diastolic bronchial tubes [31]. Therefore, the combination drug regimen can make the process of anaesthesia emergence smoother and the recovery of airway reflexes more coordinated, thus reducing the incidence of extubation cough.

This study still has some shortcomings: Firstly, it is a small-sample, single-centre clinical trial, and it only focuses on a specific type of pediatric strabismus surgery. Secondly, excluding children with preoperative crying may limit generalizability to anxious population. Thirdly, the use of sealed envelopes for randomization, while maintaining allocation concealment, is less rigorous than computer-based systems. Despite balanced baseline characteristics, future trials should adopt electronic randomization for enhanced methodological rigor. Additionally, this study mainly focused on early postoperative recovery and did not follow up on the long-term prognosis and quality of life of the patients. Finally, in addition to the currently observed indicators, further attention should be paid to the effects of anaesthesia on pediatric neurocognitive function and future studies should integrate anxiety scales for broader applicability etc., in order to provide a more personalized and scientific anesthetic strategy for pediatric anaesthesia.

In conclusion, the protocol of low-dose esketamine combined with propofol in microscopic pediatric strabismus surgery patients can effectively reduce the pain of propofol injection and early postoperative pain, decrease the incidence of perioperative adverse reactions, and promote rapid postoperative recovery of the children.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03095-x.

Supplementary Material 1

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Author contributions

The individual contributions were specified as follows: Shen Y participated in experimental design, result evaluation, formal data analysis, and manuscript writing and editing; Shi B and Mo Y were involved in data collection, patient follow-up, and anesthesia management; Wu J was responsible for drug formulation, the implementation of blinding procedures; Dr. Sun oversaw patient safety, provided overall project supervision, and served as the corresponding author for academic guidance.

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Data availability
Due to the sensitive nature of the research, the datasets supporting the findings of this study are not publicly available. However, they can be obtained from the corresponding author upon reasonable request. The data are maintained in a controlled-access repository managed by the Department of Anesthesiology, Perioperative, and Pain Medicine at the First Affiliated Hospital of Zhengzhou University.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Committee for Scientific Research and Clinical Trials of The First Affiliated Hospital of Zhengzhou University (Approval No. 2023-KY-1509), Chinese Clinical Trial Registry Identifier: ChiCTR2400092266. Prior to the commencement of the trial, patients were briefed on the protocol, and written consent was secured from every participant and their guardians. This study adhered to the guidelines established by the Consolidated Standards of Reporting Trials (CONSORT) and complied with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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