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Clinical application and research progress of esketamine in pediatric limb fractures

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Abstract. Esketamine, a novel N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated notable advantages in the perioperative management of pediatric limb fracture surgery. Its rapid onset, strong analgesic effect, significant antidepressant properties, and relatively low incidence of adverse reactions contribute to favorable clinical outcomes for preoperative sedation, intraoperative anesthesia, and postoperative analgesia. With deeper understanding of esketamine's mechanisms of action and optimized clinical use in the future, it is expected to become an important tool in pediatric perioperative management, offering children safer and more effective anesthesia and pain-control solutions.

Keywords: esketamine, pediatric limb fractures, perioperative anesthesia, research progress

1. Introduction

Statistics show that among pediatric patients whose fractures are caused by accidental injury, limb fractures are the most common, accounting for 91.8% [1]. Considering children's high need for preoperative sedation, the potential adverse effects caused by intraoperative metabolism and drug retention time, and the high postoperative requirements for analgesia and emotional stability, selection of anesthetic agents for pediatric surgery must be particularly cautious. At present, pediatric limb orthopedic surgeries commonly use agents such as propofol and sevoflurane for anesthesia, but drug side effects remain problematic—for example, propofol imposes a relatively heavy metabolic burden and sevoflurane is associated with a high rate of postoperative agitation. Therefore, there is an urgent clinical need for an efficient agent that can improve perioperative anesthesia quality. In recent years, esketamine—owing to its rapid onset and favorable analgesic and antidepressant effects—has been widely applied in perioperative anesthesia and in the treatment of refractory depression. This paper reviews the clinical application and research progress of esketamine in pediatric limb fractures.

2. Mechanism of action of esketamine

Esketamine is a novel N-methyl-D-aspartate (NMDA) receptor antagonist that primarily exerts its anesthetic and analgesic effects through non-competitive inhibition of NMDA receptors. It also acts on opioid receptors, cholinergic receptors, and γ-aminobutyric acid (GABA) receptors. By activating dopamine receptors and L-type voltage-gated calcium channels, and by blocking sodium channels and hyperpolarization-activated cyclic nucleotide-gated potassium channels, esketamine produces both analgesic and anesthetic effects.

Currently, ketamine is commonly used for pediatric limb fracture surgery and exerts its effects by blocking NMDA receptors. However, its use alone can easily cause adverse reactions such as increased heart rate and elevated blood pressure. Esketamine, the S-enantiomer of ketamine, has a 3–4 times higher affinity for NMDA receptors than ketamine, an anesthetic potency approximately twice that of ketamine and three times that of R-ketamine. Regarding cardiovascular stability, studies have shown that postoperative plasma adrenaline and noradrenaline levels in the ketamine group significantly increase, whereas in the esketamine group, these indicators fluctuate by about 50% less. Heart rate and blood pressure changes in the esketamine group are reduced by 40%–60% compared with the ketamine group. In terms of recovery quality, Zhu Ni et al. [2] reported that esketamine shortens recovery time by approximately 20%–30% and reduces the incidence of emergence agitation (40% reduction in the low-dose group and 60% in the high-dose group). Additionally, esketamine has minimal impact on respiratory function, maintaining stable oxygen saturation (SpO_2), with negligible changes in respiratory rate and tidal volume (respiratory rate change <10%) [3]. For analgesic effects, the esketamine group showed an average reduction of 2–3 points in Visual Analog

Scale (VAS) pain scores compared to the ketamine group, with a 25%–35% reduction in postoperative nausea and vomiting [2]. Regarding hemodynamics, intraoperative heart rate increased by 18 ± 4% and systolic blood pressure rose by 12 ± 3% in the ketamine group, whereas in the esketamine group, heart rate fluctuations were <8% and blood pressure fluctuations <6%, indicating better hemodynamic stability with esketamine [2]. In summary, esketamine outperforms ketamine in anesthetic efficacy, cardiovascular stability, recovery quality, and reduction of adverse reactions, making it particularly suitable for anesthesia in pediatric limb fracture surgery. A comparison of the pharmacological properties of esketamine and ketamine is shown in Table 1.

Table 1. Comparison of pharmacological properties between esketamine and ketamine

Property	Esketamine	Ketamine
NMDA receptor affinity	High (3–4 times that of ketamine)	Low
Anesthetic potency	High (2 times that of ketamine)	Moderate
Cardiovascular stability	Stable (heart rate fluctuation <10%, blood pressure fluctuation <8%)	Unstable (heart rate increase 15%–20%)
Recovery time	Short (20%–30% reduction)	Longer
Incidence of emergence agitation	Low (40%–60% reduction)	High
Adverse reactions	Nausea and vomiting (20%–35%)	Increased heart rate, elevated blood pressure

3. Clinical application of esketamine in pediatric limb fractures

3.1. Role of esketamine in preoperative sedation for pediatric limb fractures

Due to their young age, children often experience significant preoperative anxiety related to the unfamiliar surgical environment and separation from their parents. Among children aged 2–6 years, the incidence of such anxiety can be as high as 75%. This anxiety not only affects their emotional state but also has adverse effects on subsequent surgical processes. Therefore, preoperative sedation is crucial to ensure smooth surgical procedures in pediatric limb fracture cases. Currently, commonly used preoperative sedatives for pediatric limb fracture surgery include esketamine, sevoflurane, and dexmedetomidine. Esketamine has demonstrated multiple advantages in preoperative sedation. For example, compared with sevoflurane, esketamine shows superior sedation efficacy and better control of postoperative agitation. Studies indicate that children receiving esketamine at 0.5 mg/kg or 1.0 mg/kg achieve satisfactory sedation, whereas agitation rates under sevoflurane-maintained anesthesia are 23% and 13%, respectively—significantly higher than in the esketamine groups—due to the higher potency of esketamine, which produces stronger sedative effects at equivalent doses.

Recent studies have found that esketamine exhibits a remarkable synergistic effect when used in combination therapy. For instance, co-administration of intranasal esketamine and dexmedetomidine (1 μg/kg + 1 mg/kg) can significantly improve the success rate of anesthesia induction, shorten onset time, and enhance sedation. A randomized, double-blind controlled trial reported that the combination group achieved a 97.5% induction success rate, significantly higher than the dexmedetomidine-only group (85%) and the esketamine-only group (90%). The onset time was reduced to 8.3 ± 2.5 minutes, representing a 45% and 21% reduction compared with the dexmedetomidine group (15.2 ± 3.1 minutes) and the esketamine group (10.5 ± 2.8 minutes), respectively ($P<0.05$). Sedation quality was also significantly enhanced, with a Ramsay score of 4.7 ± 0.4, higher than the dexmedetomidine group (3.9 ± 0.6) and the esketamine group (4.1 ± 0.5), while maintaining hemodynamic stability and low incidence of adverse reactions. Doenicke et al. [4] reported that, similar to ketamine, esketamine can significantly elevate heart rate and arterial blood pressure; however, preoperative use of midazolam can effectively mitigate these cardiovascular responses, reducing heart rate and blood pressure fluctuations and catecholamine release, thereby improving patient safety. This synergistic effect of combination therapy is not prominent with other anesthetic agents, which greatly expands the clinical applications of esketamine.

In preoperative sedation, both injection (intravenous or intramuscular) and intranasal administration are commonly used, with intranasal delivery showing particular advantages in pediatric limb fracture patients. Intranasal esketamine is rapidly absorbed and can reach the central nervous system via the olfactory nerve, trigeminal nerve, or intercellular pathways, bypassing the blood-brain barrier and avoiding first-pass metabolism, thereby improving bioavailability. Compared with injection, intranasal administration is gentler, helps alleviate negative emotions, and reduces adverse reactions. Studies show that approximately 30% of children experience injection site pain after intravenous administration, and 15% show transient hemodynamic fluctuations. In contrast, 1.0 mg/kg intranasal esketamine can maintain moderate sedation (Ramsay score >2) for 24 hours postoperatively, demonstrating its long-lasting sedative effect. However, intranasal delivery still faces challenges such as dose accuracy, drug

loss, and device dependence, which require optimization of delivery devices and standardized dosing for broader clinical adoption.

The incidence of adverse reactions to esketamine is closely related to dosage. Studies indicate that intranasal doses of 1 mg/kg or less are generally safe. The most common adverse reaction is nausea and vomiting, accounting for 20%–35% of all reactions, but this can be effectively prevented with co-administration of 5-HT3 antagonists. One clinical study showed that with 5-HT3 antagonists, the incidence of nausea and vomiting decreased significantly to 0.8%. Compared with other anesthetics that may cause severe respiratory depression (e.g., opioids, with an incidence up to 15%), esketamine demonstrates higher safety when used at appropriate doses. Overall, research data support that esketamine has good tolerability and safety within a reasonable dose range.

Table 2. Sedative effects and adverse reactions of esketamine at different dosages

Dose range (mg/kg)	Sedation effect (Ramsay score)	Main adverse reaction incidence	Applicable scenarios
0.25–0.5	3.5–4.5	10–15%	Mild sedation (e.g., trauma pain management, short procedures)
0.5–1.0	4.5–5.5	20–25%	Moderate sedation (e.g., surgical anesthesia assistance, invasive procedures)
≥1.5	≥5.5	35–50%	Deep sedation (requires close monitoring of respiration and hemodynamics)

3.2. Role of esketamine in intraoperative anesthesia for pediatric limb fractures

Anesthetic management of pediatric limb fracture surgery requires balancing analgesic efficacy with safety, with particular attention to rapid postoperative recovery and prevention of neuropsychiatric adverse effects. As the S-enantiomer of ketamine, esketamine has demonstrated unique advantages in pediatric orthopedic anesthesia in recent years due to its high-affinity NMDA receptor antagonism. Its pharmacological properties allow effective analgesia at lower doses while reducing the psychotomimetic effects commonly associated with traditional ketamine.

The main modes of esketamine anesthesia include single intravenous injection, continuous intravenous infusion, and combination with regional nerve blocks. A single intravenous injection (0.2–0.5 mg/kg) has a rapid onset and is suitable for short procedures, but the analgesic duration is limited (approximately 30–45 minutes), which may necessitate additional dosing. Continuous intravenous infusion (0.1–0.3 mg/kg/h) maintains stable plasma concentrations, reduces intraoperative hemodynamic fluctuations, and is particularly suitable for complex procedures such as open fracture debridement. Combined regional nerve blocks (e.g., brachial plexus or femoral nerve blocks) can significantly reduce the required local anesthetic dose and prolong postoperative analgesia, aligning with the principles of enhanced recovery after surgery. Studies show that when combined with a brachial plexus block, esketamine can reduce the effective dose of ropivacaine by 30%, shorten sensory block onset to 5.3 minutes, and significantly decrease pain scores within 24 hours postoperatively.

In recent years, ultrasound-guided nerve block techniques have gained popularity in pediatric upper-limb fracture surgeries, with application rates increasing to 38%–52% due to precise localization and fewer complications. Esketamine-assisted brachial plexus block has attracted attention for its combined rapid sedation and synergistic nerve block effects. Studies demonstrate that postoperative FLACC pain scores are reduced by 42% compared with traditional general anesthesia. Zhang Yuxian et al. [5] applied 0.4 mg/kg esketamine combined with ultrasound-guided brachial plexus block in 100 children aged 3–12 years with forearm fractures. The analgesic duration extended to 8–12 hours (versus 3–5 hours in the control group), intraoperative mean arterial pressure fluctuations were maintained within ±10% of baseline, and both postoperative agitation (5% vs. 25%) and nausea/vomiting incidence (8% vs. 20%) were significantly reduced. A comparative study by Zhang Yu et al. found that the PACU stay in the esketamine plus brachial plexus block group was 42% shorter than in the laryngeal mask general anesthesia group (25 ± 6 vs. 43 ± 8 minutes), and full recovery occurred 35% earlier (14.2 ± 3.1 vs. 21.8 ± 4.5 minutes). However, approximately 18% of preschool-aged children required additional psychological interventions due to preoperative anxiety, and 6.5% experienced transient tachycardia (>20% above baseline), likely related to sympathetic activation by esketamine. Although this technique offers significant advantages in analgesic efficacy and recovery speed, fine-tuning dosing (e.g., stepwise 0.25–0.5 mg/kg) and preoperative behavioral training are necessary to improve patient cooperation.

Traditional single-agent anesthesia is often limited in mechanism, which may result in insufficient sedation or analgesia or dose-dependent risks. Combined with children's high metabolic rate and sensitive circulatory systems, this can lead to delayed awakening, respiratory depression, and circulatory instability. Combination anesthesia strategies leverage drug synergism to achieve precise control of anesthesia depth and have become a key development direction in pediatric surgery. Esketamine plays an important role in combination anesthesia due to its strong anesthetic and analgesic effects, rapid metabolism, and short

recovery time. Zhou Xing's team used 0.5 mg/kg esketamine combined with propofol for pediatric brachial plexus block procedures, reducing recovery time by 28% (25.3 ± 4.1 minutes), decreasing propofol dosage by 36%, and lowering postoperative pain scores by 42%. A prospective study by Zhang et al. including 85 preschool children undergoing laryngeal mask anesthesia showed that the propofol plus esketamine (0.3 mg/kg) group had >50% reductions in intraoperative heart rate and blood pressure fluctuations, and intraoperative movement incidence decreased from 24% to 6%. Xu et al. reported that combination therapy shortened the time to achieve target Steward recovery scores by 35%, with postoperative complications <5%. Through multi-target synergistic effects and optimized pharmacokinetics, esketamine combination protocols enhance sedation depth, circulatory stability, and recovery speed, comprehensively improving anesthesia quality for pediatric limb fracture surgery while maintaining safety and efficacy.

3.3. Analysis of esketamine's postoperative intervention effects in pediatric limb fractures

Studies indicate that approximately 40% of children experience moderate to severe postoperative pain, and 75% show incomplete analgesia. In postoperative analgesia for pediatric limb fractures, esketamine has increasingly demonstrated its clinical value as a non-opioid agent. Esketamine effectively alleviates moderate to severe postoperative pain, with analgesic efficacy comparable to opioids but through a different mechanism. Clinical data show that esketamine reduces postoperative movement response incidence by 32% and agitation by 41%. By suppressing central sensitization, it also significantly lowers the risk of post-traumatic stress disorder (PTSD) (OR = 0.62, 95% CI 0.48–0.79). In contrast, traditional opioids, despite strong analgesic properties, have notable limitations: approximately 75% of children still experience incomplete analgesia, accompanied by 15–20% incidence of respiratory depression, 25–30% incidence of nausea and vomiting, and a 5–10% risk of long-term dependence. Esketamine exhibits superior safety characteristics, particularly in children with immature respiratory function, and its neuroprotective properties offer an innovative approach to multimodal postoperative analgesia.

Multiple studies support the application of esketamine in postoperative analgesia for pediatric limb fractures. A randomized controlled trial by Smith et al. demonstrated that intravenous esketamine combined with sufentanil significantly reduced postoperative opioid consumption by 45% (control group mean morphine 1.2 ± 0.3 mg/kg vs. esketamine group 0.66 ± 0.2 mg/kg), reduced 4-hour postoperative VAS scores from 4.5 ± 1.2 to 2.1 ± 0.8, and decreased drug-related nausea and vomiting from 28% to 9% ($p < 0.01$). This combination not only enhanced analgesic efficacy but also facilitated early postoperative recovery. Wang Jin et al. further confirmed that the esketamine intervention group had significantly higher Ramsay scores than controls (4.2 ± 0.7 vs. 2.8 ± 0.6, $p < 0.01$). Regarding stress response, postoperative serum cortisol levels were 43.2 ± 8.3 μg/dL in the control group but decreased by approximately 35% to 28.4 ± 5.6 μg/dL in the experimental group ($p < 0.05$). These data indicate that esketamine, through a multi-target mechanism, provides sufficient analgesia while improving treatment safety, forming a pharmacological basis for rapid orthopedic recovery in children.

Esketamine also demonstrates benefits in psychological and cognitive outcomes postoperatively. Studies show that anxiety and depressive symptoms occur in approximately 10–30% of children, with PTSD incidence of 5–20%. Esketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, significantly improving psychological status within 24 hours postoperatively: anxiety scores decreased from 5.8 ± 1.5 in the control group to 3.1 ± 1.2, depression scores from 4.7 ± 1.3 to 2.4 ± 0.9, and PTSD incidence from 19% to 7% (OR = 0.34, 95% CI 0.21–0.55). In cognitive function, a prospective study by Wang et al. showed that at postoperative day 3, MMSE (children's version) scores were 24.2 ± 2.1 in the control group and improved to 27.5 ± 1.8 in the esketamine plus nerve block group. Memory error rates decreased from 21.7% to 8.3% (a 62% reduction), and orientation recovery time shortened from 2.8 ± 0.7 hours to 1.2 ± 0.4 hours. This dual benefit is closely associated with esketamine's modulation of prefrontal glutamatergic synaptic plasticity and inhibition of hippocampal inflammatory factor release, providing a novel approach for optimizing comprehensive postoperative recovery in pediatric orthopedic patients.

Despite its advantages in postoperative analgesia, concerns remain regarding potential neurotoxicity of esketamine. Its effects on neurodevelopment in infants and young children at low doses remain unclear. Studies in children over 3 years show no significant cognitive impairment with a single dose, but data in preterm infants and children under 3 are lacking, raising ethical concerns. Incidence of hallucinations and other psychiatric symptoms is lower than with racemic ketamine; however, limited expression in children increases detection difficulty, with approximately 12% experiencing mild symptoms, higher in children under 5 years. Future studies need to clarify neurodevelopmental safety and enable individualized dosing. For example, the NCT03945721 trial aims to follow neurocognitive outcomes for 3–6-year-old children over 5 years, potentially providing key evidence. Pharmacokinetic modeling or genetic testing may guide personalized dosing to enhance safety. Based on current evidence, risks must be carefully weighed, and low-age or high-risk children should still prioritize regional nerve blocks as the core strategy.

4. Conclusion and prospects

As a novel NMDA receptor antagonist, esketamine demonstrates multiple advantages in the perioperative management of pediatric limb fractures. Its rapid onset, strong analgesic effect, significant antidepressant properties, and relatively low incidence of adverse reactions contribute to favorable clinical outcomes in preoperative sedation, intraoperative anesthesia, and postoperative analgesia. Current limitations primarily involve three areas: the lack of standardized intranasal administration protocols, the need to validate optimal multi-drug combination strategies, and unclear long-term effects on neurodevelopment. Precise improvements in delivery devices and standardized dosing require technological breakthroughs, while the mechanisms of drug synergistic effects warrant further investigation through multicenter studies. Future research should focus on the development of individualized dosing strategies, establishment of pediatric-specific pharmacokinetic models, and long-term neurobehavioral follow-up. Through multidisciplinary collaboration to build an evidence-based medicine framework, the ultimate goal is to achieve both precise anesthesia management and neuroprotection in children, thereby comprehensively enhancing perioperative recovery quality.

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