



Progress in the Application of Esketamine in Pediatric Anesthesia

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Abstract

As a sedative and analgesic drug, esketamine is widely used in clinical anesthesia. Due to its separation anesthesia, it is particularly suitable for pediatric anesthesia and analgesia. It can not only alleviate the separation anxiety of children, promote smooth separation between children and parents, avoid mental harm to children, but also facilitate relatively stable anesthesia induction. Currently, esketamine is widely used in emergency procedural sedation and analgesia, preoperative sedation, anesthesia outside the operating room, general anesthesia, and regional anesthesia as adjuvant medication. This article reviews the current application status and adverse reactions of esketamine in pediatric anesthesia, providing reference for the application and research of esketamine in pediatric anesthesia.

Keywords

Esketamine, Pediatric Anesthesia, Sedation and Analgesia, Preoperative Anxiety, Regional Anesthesia

Introduction

Esketamine, also known as right-handed ketamine, is the enantiomer of ketamine. It antagonizes N-methyl-D-aspartate (NMDA) receptors, inhibits the information transmission of injury by spinal dorsal horn and peripheral NMDA receptors, and produces anesthetic and analgesic effects. It has a higher affinity for NMDA receptors and opioid μ receptors, and has stronger analgesic efficacy than ketamine. It has a higher clearance rate in the body, faster recovery time, and lower incidence of side effects. It has gradually replaced ketamine and is widely used in clinical anesthesia and analgesia [1-5]. Ketamine was introduced for clinical use in children in 1998 and is currently the only sedative drug that can be administered intramuscularly in clinical anesthesia. It is highly suitable for children who

have difficulty receiving injections before surgery. Studies have shown that compared with other sedatives, esketamine has good sedative and analgesic effects, with less impact on respiratory and circulatory functions, and is more suitable for pediatric clinical sedation and analgesia [6].

Clinical Pharmacology

Ketamine is a water-soluble derivative of cycloheximide, which contains a chiral carbon center and achieves two different spatial configurations, S-ketamine and R-ketamine. The two enantiomers have different affinities for different receptors. Ketamine mainly exerts its effects by antagonizing NMDA receptors, inhibiting the thalamus neocortex system, selectively blocking pain sensation, and exerting

analgesic effects; on the other hand, ketamine has an excitatory effect on the limbic system, causing loss of pain sensation, blurred consciousness, and delayed response to stimuli from the surrounding environment, resulting in a state of separation between consciousness and sensation. Due to its characteristic of separating anesthesia, ketamine has been widely used in clinical anesthesia and analgesia [7].

Esketamine is the right-handed enantiomer of ketamine, with a mechanism of action similar to ketamine. It exerts hypnotic, sedative, and analgesic effects by interacting with NMDA receptors, opioid receptors, M-cholinergic receptors, monoamine receptors, adenosine receptors, and other purine receptors [8]. Esketamine has a higher affinity for NMDA receptors and opioid μ receptors, and has stronger analgesic efficacy than ketamine.

Its analgesic effect is twice that of ketamine and four times that of R-ketamine. The dosage used is only half that of ketamine, with mild respiratory depression and higher clearance rate in the body. The incidence of side effects such as nausea, hypertension, and tachycardia is lower, and the recovery time is shorter [9,10]. In clinical practice, esketamine can be administered through different routes, such as nasal drops, rectal administration, intravenous injection, sacral injection, epidural injection, and so on.

Application in Clinical Anesthesia

Emergency Procedural Sedation and Analgesia:

In emergency medical units, due to the lack of knowledge and experience in pain management for children, their pain often does not receive timely treatment [11]. Opioids are commonly used painkillers in emergency departments, but due to concerns about their side effects such as respiratory and circulatory suppression, they are rarely used in the treatment of children [12]. Due to its characteristic of isolated anesthesia, esketamine provides strong pain relief and sedation while maintaining stable spontaneous breathing and cardiopulmonary function, preserving protective airway reflexes.

Serious side effects such as salivation, nausea and vomiting, and central nervous system phenomena are

very rare [13]. It is estimated that the incidence of laryngeal spasms is about 0.4%–0.7% [14], while the frequency of psychogenic reactions such as hallucinations is much lower than that of adults [15].

A nationwide study conducted in Germany surveyed 305 children's hospitals, and approximately 86.2% of hospitals used ketamine or esketamine for procedural sedation and analgesia [16]. Another study showed that the most commonly used medication for pediatric patients receiving procedural sedation and analgesia in emergency medical units is ketamine (42.4%), with an adverse event rate of only 3% [17]. Dhawal Patel et al. [18] found that intravenous injection of 1–1.5 mg/kg esketamine can be safely used for emergency procedural sedation and analgesia in children with forearm fractures.

Preoperative Sedation:

Pain, fear, anxiety, and anger are the main emotions that children experience when receiving medical treatment [19]. It is estimated that about 60–70% of children show significant anxiety before surgery [20,21]. High preoperative anxiety may lead to difficulties in inducing inhalation anesthesia in children, and violent inhalation anesthesia induction may increase the incidence of postoperative agitation and even lead to changes in postoperative bad behavior [22], which has a series of negative effects on the growth and development of children. Esketamine nasal spray has slight irritation to the nasal mucosa, can be quickly absorbed, and plays an analgesic and sedative role. It can not only reduce the separation anxiety of children before surgery and reduce restlessness but also has no side effects such as respiratory inhibition.

Liu W et al. [23] randomly divided 96 preschool children undergoing ophthalmic surgery into three groups. Children in group C were given nasal drip of normal saline, children in group S2 were given undiluted original solution of esketamine (concentration: 25 mg/ml), and children in group S1 were given two times of normal saline diluted esketamine (concentration: 12.5 mg/ml). The volume of nasal spray received by three groups of children was 0.4 ml/kg. Esketamine or saline was sprayed into the child's nostrils 10 minutes before anesthesia induction,

accompanied by parents. The results showed that 0.5–1 mg/kg esketamine nasal spray could significantly reduce separation anxiety of children undergoing strabismus surgery, reduce postoperative restlessness, and would not cause respiratory depression.

Lu X et al. [24] found that nasal drops of 1 µg/kg dexmedetomidine combined with 0.5 mg/kg esketamine can significantly improve the compliance of pediatric patients with inhalation anesthesia masks, increase the success rate of sedation, and reduce the incidence and severity of postoperative agitation. Su Yingying et al. [25] studied the half effective dose (ED₅₀) of esketamine for preoperative sedation in children, and the results showed that the ED₅₀ of esketamine was 0.58 mg/kg, and the ED₉₅ was 0.618 mg/kg.

Anesthesia Outside the Operating Room:

Extracorporeal anesthesia includes various non-invasive examinations and treatments, such as painless gastroscopy, painless fiberoptic bronchoscopy, interventional diagnosis and treatment, ultrasound, and magnetic resonance imaging. Children may not be able to cooperate with these examinations and treatments due to their incomplete mental development, crying, and fear. Esketamine has good sedative and analgesic effects, minimal impact on breathing, fast recovery, and few adverse reactions, playing an indispensable role in such procedures.

The consensus among pediatric outdoor anesthesia experts indicates that intravenous injection of 0.5–1 mg/kg esketamine can achieve good sedative effects; intravenous injection of 1–2 mg/kg can achieve general anesthesia without significant respiratory inhibition. The onset time after intravenous injection is 1 minute, and the complete recovery time is 50–110 minutes. The main adverse reaction is an increase in airway secretions, which usually requires combination with anticholinergic drugs such as atropine. Su et al. [26] studied 26 children undergoing painless gastroscopy and found that the half effective dose of esketamine combined with 3 mg/kg propofol was 0.143 mg/kg, showing good sedative effect and high safety.

Zheng X et al. [27] found that the success rate of endoscopic implantation in children receiving 0.5

mg/kg esketamine with 2 mg/kg propofol was higher than that of 0.2 mg/kg nalbuphine, with less propofol dosage and more stable hemodynamics. However, the esketamine group had a higher incidence of recovery agitation and diplopia. Wang J et al. [28] compared different esketamine doses in pediatric gastroscopy. The 0.7 mg/kg dose had the highest implantation success rate, more stable hemodynamics, less additional propofol use, and improved endoscopist satisfaction.

General Anesthesia:

The use of esketamine for general anesthesia in children can enhance sedation and analgesia, reduce central nervous system sensitization, opioid-induced tolerance and hyperalgesia, decrease the consumption of anesthetics and analgesics, and prevent postoperative agitation [29]. Van de Bunt et al. [30] conducted a retrospective study on 57 children with intussusception who underwent radiation reduction. Among them, 20 patients received esketamine sedation and 37 received morphine. The esketamine group (0.5–1.0 mg/kg) had a higher success rate of surgery, lower recurrence rate, and shorter operation and hospitalization time compared to the morphine group (0.05–0.1 mg/kg).

Becke K et al. [31] randomly divided 36 children undergoing major urological surgery into an esketamine group and a control group. The esketamine group received 0.2 mg/kg intravenously after intubation, followed by continuous infusion of 5 µg/kg/min. The control group received saline. The first PCA compression time in the esketamine group was 62 minutes, compared to 37 minutes in the control. There was a slight reduction in morphine use within the first 36 hours, though no significant difference was noted over 72 hours. This suggests low-dose esketamine has additional sedative effects but may not reduce overall postoperative pain or morphine use.

Liu F et al. [32] studied 200 children undergoing tonsillectomy, divided into esketamine and fentanyl groups. Three to five minutes before surgery, patients received either 2 µg/kg fentanyl or 1 mg/kg esketamine intravenously. Postoperative levels of c-fos and c-jun mRNA were significantly lower in the esketamine group ($P < 0.05$). FLACC scores at 1 and 24 hours were also lower. The results indicated that esketamine could

alleviate pain and inflammatory response and reduce remifentanyl-induced hyperalgesia when combined with remifentanyl.

Regional Anesthesia Adjuvant Medication:

In pediatric regional blocks, adjuvants are often added to prolong analgesic time, enhance analgesia, reduce monotherapy doses, and lower adverse reaction rates. Esketamine exerts its analgesic effect via NMDA or opioid receptors in the spinal cord [33]. It has strong sedative and analgesic properties, contains no preservatives, and shows no neurotoxicity [34,35]. It has been used as a spinal anesthesia substitute in children. Compared with traditional anesthetics, esketamine for sacral block avoids serious cardiovascular or central nervous system complications from accidental vascular injection [36].

Studies show that in pediatric sacral block, ketamine alone provides analgesia comparable to bupivacaine [37]. Weber F et al. [38] divided 30 children undergoing inguinal or penile surgery into Group B (0.125% bupivacaine 1 ml/kg) and Group K (0.5 mg/kg esketamine + 0.125% bupivacaine 1 ml/kg). Within 24 hours postoperatively, 67% of children in Group K needed no further analgesia compared to only 20% in Group B. No significant adverse effects were observed in either group.

De Negri et al. [39] found that adding 0.5 mg/kg esketamine to 0.2% ropivacaine enhanced analgesia duration and effectiveness with no notable side effects. S. J. Martindale et al. [40] reported that sacral esketamine combined with bupivacaine prolonged analgesia by 6 hours and reduced postoperative analgesic needs by over 50% compared to bupivacaine alone or intravenous esketamine + sacral bupivacaine.

Summary

As a right-handed enantiomer of ketamine, esketamine has better analgesic and sedative effects with lower adverse reactions. It plays an important role in pediatric emergency, anesthesia, and pain management, improving the success rate of outdoor examinations in children, reducing preoperative anxiety, facilitating the successful implementation of anesthesia induction, and reducing the incidence of

postoperative adverse behavioral reactions in children. At present, there is still limited research on the application of esketamine in children. In the future, more multi-center and large-sample studies can be conducted to provide stronger evidence for the clinical application of esketamine in children.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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