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Progress in clinical application of esketamine in pediatric anesthesia

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Abstract: Ketamine is a commonly used anesthetic drug, but its clinical use declined in the late 1990s due to its postoperative nightmares, extrapyramidal syndrome, and a tendency to abuse. As an isomer of ketamine, esketamine is applied in a small dose than racemic ketamine, with strong analgesic and sedative effects, fewer cardiovascular and psychiatric adverse reactions. It has a significant application value in pediatric anesthesia with fast metabolism and high clearance rate *in vivo,* slight impact on children's respiratory and circulation, and rapid awakening and recovery.

Keywords: Esketamine; Children; Sedation; Diagnostic procedures; Anesthesia induction; Pre-hospital emergency analgesia; Postoperative analgesia

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Esketamine is a multi-target drug that interacts with the N-methyl-D-aspartic acid (NMDA) receptor, opioid receptor, cholinergic receptor, monoamine receptor, sodium and calcium channels to produce hypnotic, sedative and analgesic effects. Esketamine has a rapid onset of action, higher potency, faster clearance and requires lower doses. It has minimal effects on respiratory circulation in pediatric patients, with rapid awakening and recovery. Therefore, it has significant application value in pediatric anesthesia. Additionally, its neuroprotective properties, bronchodilatory effects, and anti-nociceptive actions provide more options for its clinical use. In this article, we discuss the pharmacological characteristics of esketamine and its indications in pediatric clinical applications, aiming to provide references for its clinical use.

1 Pharmacological properties of esketamine

Esketamine is the levoisomer of ketamine [1], with an average elimination half-life of about 4 hours and a distribution volume of 5-10 L/kg. It is mainly metabolized by cytochrome (CYP) 450, with demethylation as the primary metabolite, and approximately 78% is excreted in the urine. Esketamine intravenous infusion takes effect within 30 seconds, reaching peak blood concentration in 1 to 2 minutes, with effects lasting 30 to 45 minutes. It can be administered through various routes such as intramuscular injection, oral, and intranasal administration. The bioavailability of intramuscular, oral, and intranasal administration is 93%, 16%-24%, and 45%-50%, respectively. The clearance of ketamine was 14.8 mg/(kg·min), while that of esketamine was 26.3 mg/(kg·min). Esketamine metabolites have a faster plasma clearance, resulting in faster recovery after a single intravenous dose. Therefore, esketamine is more controllable in anesthesia and perioperative analgesia, providing patients with rapid and comfortable recovery. The loss of consciousness and analgesic effects of esketamine are dose-dependent. The blood concentration required for analgesic effects is much lower than that required for loss of consciousness. The minimum blood concentration required for pediatric general anesthesia is 0.4-2.0 mg/L, while a concentration ≥0.05 mg/L can increase the pain threshold. Therefore, the analgesic effect can persist after the anesthesia effect fades.

1.1 Effects on the NMDA receptors

Ketamine contains two stereoisomers, S(+) ketamine and R(−) ketamine, which can competitively antagonize the binding site of phencyclidine (PCP) on the NMDA receptor in the central nervous system [2]. Compared to the R(−)isomer, esketamine has approximately four times higher affinity/potency for the PCP site of NMDA receptors, which is twice that of the racemic mixture. NMDA receptors, composed of two GluN1 and two GluN2 subunits, are widely expressed in pain transmission pathways such as the brain, spinal cord, and dorsal root ganglia. Their activation is involved in pain transmission. Esketamine can act as a receptor channel blocker (effectively shortening the opening time) and as an allosteric modulator, reducing the frequency of channel opening. It can slowly dissociate from receptors (even after glutamate dissociation), resulting in prolonged blockade and extended channel blocking time. Pain stimuli can lead to sustained over-activation of sensitive synapses of pain-transmitting C-fibres in the dorsal horn

of the spinal cord, leading to excessive entry of calcium ions into neurons and activation of protein kinase C (PKC), resulting in phosphorylation of NMDA receptors [3]. Inhibiting NMDA receptors can directly block the pain transmission pathway, reduce calcium influx, and block the pain transmission pathway directly.

Activation of NMDA receptors is involved in the development of spinal hyperexcitability and persistent pain [4]. Esketamine can effectively prevent the development of long-term potentiation (LTP) induced by pain stimulation. In addition to phosphorylating NMDA receptors, PKC may regulate the function of NMDA receptors by participating in interactions with postsynaptic density and cytoskeletal proteins, especially postsynaptic density protein-95 (PSD95), which interacts with NMDA receptors and may participate in the processing of spinal nociceptive signals [5]. Esketamine can block NMDA receptors and the pathological changes mentioned above, reduce central nervous system sensitization reactions, and prevent acute pain from becoming chronic and pain memory from developing.

1.2 Effect on opioid receptors

The binding affinity of esketamine for μ and κ receptors is 2 to 4 times that of R(−) ketamine [6]. Naloxone is a μ receptor-specific antagonist with weak effects on δ and κ receptors. At high doses, naloxone can only partially antagonise the analgesic effects of esketamine. The mechanism by which esketamine induces hallucinations may involve κ receptor activation. Opioids can promote the excitability of NMDA receptors by activating μ receptors, inducing pain hypersensitivity associated with LTP. Esketamine can improve function of μ receptor, and pre-injection of low-dose esketamine before using opioids can prevent pain hypersensitivity.

1.3 Effects on the cholinergic and adrenergic receptors

The affinity of esketamine for M cholinergic receptors is three times that of R(−) ketamine. Esketamine can inhibit the reuptake of dopamine and serotonin (5-HT), possibly enhancing the activity of central dopaminergic neurons. Esketamine can cause catecholamine release, inhibit norepinephrine reuptake, activate the sympathetic nervous system indirectly, and causing cardiovascular stimulation, leading to increased blood pressure and heart rate. It enhances the bronchodilator effect of catecholamines, improving lung compliance in patients with reactive airway disease or bronchospasm. Esketamine can relieve pain by activating descending pain inhibitory pathways by enhancing the monoaminergic system or by directly activating corresponding brain areas. Low-dose esketamine can activate regions of descending inhibitory pathways such as the anterior cingulate cortex, insula, prefrontal cortex and brainstem in healthy volunteers, which correlates with pain scores. Pretreatment with α 2-adrenergic receptor antagonists or 5-HT receptor antagonists can completely reverse the analgesic effects of ketamine [7-8]. Its sedative and analgesic effects may be related to the regulation of the cholinergic and adrenergic systems, leading to sensitization of the opioid system and enhancement of the activity of endogenous analgesic systems.

1.4 Other receptors

Esketamine can produce local anesthetic effects by blocking voltage-gated sodium ion channels. It can directly antagonize the bronchospasm induced by histamine on bronchial smooth muscle and relax airway smooth muscle by blocking L-type calcium ion channels. The hypnotic effect of esketamine is attributed to its blockade of hyperpolarization-activated cyclic nucleotide-gated ion (HCN) channels, which are involved in and mediate hyperpolarization (HCN-1 is mainly expressed in the cortex, affecting neuronal excitability by altering cell resting potential and membrane resistance) [9].

1.5 Neuroprotective effects

Activation of NMDA receptors is crucial in the pathophysiological process leading from ischemia to apoptosis, and antagonizing NMDA receptors inhibits calcium influx into cells, reducing glutamate-induced neurotoxicity and exerting a protective effect on neurons. Diffuse cortical depolarization can occur in patients with severe traumatic brain injury (with an incidence of 54% to 100%), with these depolarizations spreading throughout the cortex at a rate of 2-7 mm per minute, leading to decoupling of neurovascular coupling and thus causing brain damage [10]. Studies have shown that esketamine can reduce the process of diffuse depolarization [11]. Esketamine has anti-inflammatory effects and can alleviate neural damage and tissue pain caused by inflammatory reactions, exerting a neuroprotective effect [12]. The neuroprotective properties of esketamine may be related to the early regulation of balance between pro-apoptotic and anti-apoptotic proteins [13].

2 Clinical application of esketamine

2.1 Application in sedation

Due to fear of the hospital environment and surgery, over half of children exhibit significant anxiety before surgery, making preoperative sedation necessary. Preoperative administration of dexmedetomidine 1 μg/kg combined with esketamine 0.5 mg/kg nasal drops in children yields better anesthetic induction effects, shorter sedation onset time, higher success rates (90%), and lower incidence of agitation after anesthesia [14]. For pediatric patients undergoing outpatient dental surgery, preoperative esketamine 0.5 mg/kg nasal drops

significantly shorten the onset time of sedation compared to dexmedetomidine nasal drops, with significant analgesic effects during and after surgery, high patient satisfaction, and completion rates [15]. For children receiving 0.5 mg/kg oral midazolam, the ED_{95} of esketamine nasal drops is 1.99 mg/kg [95% CI, 1.95- 2.01 mg/kg]. Combined therapy not only improves patients' satisfaction with sedation, but also does not increase awakening time or the incidence of adverse events [16]. Preoperative esketamine 0.25 mg/kg nasal drops can reduce the ED_{90} dose of oral midazolam by approximately 45.2% (0.461-0.253 mg/kg), shorten sedation onset time and postoperative recovery time, and reduce the incidence of adverse events caused by the use of midazolam alone [17]. In children with coronary artery disease, esketamine used for preoperative sedation has an ED_{50} of 0.7 mg/kg when administered nasally, with a sedation onset time of (16.39 ± 7.24) minutes, which is safe and effective [18]. Combined use of esketamine with dexmedetomidine or midazolam, and other drugs for sedation in pediatric emergencies is safe and effective. This regimen can shorten the onset time of sedation, reduce the side effects of using a single sedative, and improve the comfort and satisfaction of children during the diagnostic and therapeutic process.

2.2 Applications in diagnostic and therapeutic procedures

Esketamine intravenous infusion takes effect in 30 seconds, has a short elimination half-life, rapid awakening, mild respiratory depression, intrinsic sympathetic activity, and fewer psychiatric side effects, making it suitable for various clinical diagnostic and therapeutic procedures. In pediatric upper gastrointestinal endoscopy under sedation, low-dose esketamine [ED_{50} 0.143 mg/kg (95% CI 0.047- 0.398 mg/kg)] combined with propofol (3 mg/kg) achieves satisfactory sedation effects, with good safety and feasibility [19]. Esketamine 0.7 mg/kg combined with propofol 3 mg/kg can improve the tolerance of school-age children during endoscope insertion (initial insertion success rate of 83.30%), maintain hemodynamic stability in children, reduce the number of additional doses of propofol and the total dose of propofol, and increase the satisfaction of endoscopists [20]. A multicenter study involving 200 pediatric patients found that the success rate of initial endoscope placement in the esketamine group (esketamine 0.5 mg/kg, propofol 2 mg/kg) was higher than that in the nalbuphine group (nalbuphine 0.2 mg/kg, propofol 2 mg/kg) (97% *vs* 66%, $P<0.01$) [21]. For pediatric patients undergoing flexible fiberoptic bronchoscopy (FFB) examination, Zhong *et al*. [22] found that the use of subanesthetic doses (0.3 mg/kg) of esketamine combined with propofol/remifentanil resulted in faster onset time, more stable intraoperative hemodynamics, and lower score on the postoperative Pediatric Anesthesia Emergence Delirium (PAED) scale. The incidence of propofol injection pain during anesthesia induction in the esketamine group was significantly reduced. Esketamine combined with midazolam can provide deep awake sedation without intubation for children undergoing cardiac catheterization [23]. Compared with propofol alone, the combination of esketamine and propofol results in faster recovery and better quality of awakening for pediatric MRI [24]. The combined use of esketamine with other sedatives helps improve the success rate of diagnostic and therapeutic procedures, stabilize hemodynamics, and enhance the safety of moderate and deep sedation and anesthesia, as well as the quality of postoperative recovery.

2.3 Application in pre-surgery and anesthesia

The NMDA glutamate transmission system is directly involved in inflammatory cascade responses, including peripheral nerve sensitization, spinal cord sensitization, glial activation, and reflex mechanisms[25][2]. Studies have shown that preoperative use of esketamine can reduce postoperative pain and promote recovery by regulating acute inflammatory reactions and stress-induced immune dysregulation caused by surgery [26-27]. In children undergoing laparoscopic tonsillectomy, the group induced with preoperative esketamine (1 mg/kg) anaesthesia had significantly lower levels of c-fos mRNA, c-jun mRNA and FLACC (Face, Legs, Activity, Cry, Consolability) scores after surgery compared to the group induced with fentanyl anaesthesia [28]. FOS and JUN proteins can sensitively and quantitatively reflect stress levels. Preoperative use of esketamine can improve postoperative stress responses and pain. An anesthesia induction regimen with0.5 mg/kg esketamine, 5% sevoflurane, and 10 μg/kg alfentanil can improve intubation conditions in children, maintaining stable spontaneous respiration and hemodynamics [29]. In children aged 7-12 years, using esketamine in combination with propofol and sufentanil at doses not exceeding 0.5 mg/kg does not increase intraocular pressure (IOP) compared to the pre-induction state [30]. This combination can inhibit the increase in IOP caused by laryngeal mask insertion. When used in pediatric forearm fracture surgery, esketamine has effects on sedation and analgesia comparable to the use of nitrous oxide combined with intranasal morphine [31]. Compared to morphine, intraoperative use of esketamine in children undergoing reduction of intussusception leads to higher success rates, lower recurrence rates, and shorter recovery and hospital stay times [32]. Administering esketamine (0.2 mg/kg) at the end of anesthesia can effectively reduce the incidence and severity of emergence delirium (ED) in pre-school children undergoing tonsillectomy and/or adenoidectomy, without prolonging extubation time or increasing adverse events [33]. Esketamine has a high level of safety and efficacy and positively impacts postoperative recovery in children. Therefore, its use should be considered as an option for anesthesia management in clinical practice.

2.4 Prehospital emergency analgesia

Children requiring rapid and effective analgesia for acute traumatic pain (such as fractures, burns, scalds) during prehospital emergency care (ED) need prompt treatment. Nasal administration of esketamine in 88% of ED patients can reduce VAS pain scores to clinically significant levels [34]. Nasal administration of 1.0 mg/kg esketamine can provide effective analgesia for 30 minutes for children aged 3-13 with moderate to severe (VAS ≥ 6/10) pain in the ED, with high patient satisfaction and mild and transient adverse reactions [35]. Children aged 4 months to 16 years using esketamine (4 mg/kg) combined with midazolam inhalation can rapidly relieve pain, improve child cooperation by reducing anxiety, and no respiratory, circulatory depression, or excessive sedation were observed even after repeated administration [36]. In situations where establishing a intravenous line is difficult, intranasal esketamine administration is a reliable and minimally invasive route of administration that provides effective and rapid analgesia for patients with ED.

2.5 Postoperative analgesia

Nasal esketamine drops can improve pain symptoms, shorten recovery time, and promote the formation and shedding of pseudomembranes in children after tonsillectomy [37]. A prospective, randomized, double-blind study of children aged 1-5 years with burns covering up to 10% of the total body surface area showed that oral midazolam and esketamine provide good analgesic effects. Continuous intravenous infusion of esketamine (initial dose of esketamine 0.3 mg/kg, maintenance dose of esketamine 0.15 mg/kg/h combined with flurbiprofen ester 5 mg/kg) after urethroplasty can provide effective analgesia in children after surgery, significantly reducing the incidence of hypotension and respiratory depression, and significantly shortening the time to first bowel movement [38]. Esketamine can provide safe and effective analgesia for children after surgery through multiple pathways, reducing postoperative adverse reactions, accelerating postoperative recovery, and providing new clinical ideas for multimodal analgesia in children after surgery.

2.6 Intraspinal application

Esketamine does not contain preservatives and can be used alone or in combination with other local anesthetics for intraspinal anesthesia. Giving the same dose of esketamine, caudal anesthesia provides longer analgesia time than intramuscular injection. During pediatric inguinal hernia repair, epidural injection of esketamine 1 mg/kg can provide analgesia for 8.8 hours, and using esketamine alone is equivalent to 0.25% bupivacaine (0.75 mg/kg) for analgesia during and after surgery [39]. Combining esketamine (0.5 mg/kg) and 0.2% ropivacaine (2 μg/kg) for epidural anesthesia can provide approximately 12 hours of postoperative analgesia with no significant side effects [40]. Esketamine at 1.0 mg/kg combined with 1 or 2 μg/kg clonidine for caudal block can provide 24 hours of perioperative analgesia for children with minimal side effects.

3 Conclusion

Esketamine, as the only intravenous anesthetic that can maintain spontaneous respiration and has sedative and analgesic effects, has significant value in pediatric sedation, anesthesia application, and emergency pain management. Esketamine, with its advantages of diverse routes of administration, controllability, and few side effects, can be widely used in pediatric clinical practice. In the future, multicenter clinical randomized controlled studies can further explore the application of esketamine in more areas, providing new ideas for personalized treatment for children.

There is no conflict of interest

References

[1] Gong XY,Weng LY,Guo DD,et al.Effect of low-dose esketamine on intravenous anesthesia of propofol combined with remifentanil during painless gastroenteroscopy[J].Chin J Clin Res, 2022,35(1):61-65. **[In Chinese]**

[2] Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors[J]. Anesthesiology, 1997, 86(4): 903-917.

[3] Benrath J, Brechtel C, Stark J, et al. Low dose of S(+)-ketamine prevents long-term potentiation in pain pathways under strong opioid analgesia in the rat spinal cord in vivo[J]. Br J Anaesth, 2005, 95(4): 518-523.

[4] Zhao RL,Liang LL,Wang LM,et al.Efficacy of low-dose esketamine on postoperative analgesia in patients undergoing thoracoscopic radical resection of lung cancer[J]. J Clin Pract Diagn Ther, 2023,37(3):269-272. **[In Chinese]**

[5] Tao YX, Huang YZ, Mei L, et al. Expression of PSD-95/SAP90 is critical for N-methyl-D-aspartate receptor-mediated thermal hyperalgesia in the spinal cord[J]. Neuroscience, 2000, 98(2): 201-206.

[6] Hirota K, Okawa H, Appadu BL, et al. Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells[J]. Anesthesiology, 1999, 90(1): 174-182.

[7] Koizuka S, Obata H, Sasaki M, et al. Systemic ketamine inhibits hypersensitivity after surgery via descending inhibitory pathways in rats[J]. Can J Anaesth, 2005, 52(5): 498-505.

[8] Niesters M, Khalili-Mahani N, Martini C, et al. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers[J]. Anesthesiology, 2012, 117(4): 868-877.

[9] Zhou C, Douglas JE, Kumar NN, et al. Forebrain HCN1 channels contribute to hypnotic actions of ketamine[J]. Anesthesiology, 2013, 118(4): 785-795.

[10] Dreier JP, Fabricius M, Ayata C, et al. Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group[J]. J Cereb Blood Flow Metab, 2017, 37(5): 1595-1625.

[11] Hertle DN, Dreier JP, Woitzik J, et al. Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury[J]. Brain, 2012, 135(Pt 8): 2390-2398.

[12] Wang CQ, Ye Y, Chen F, et al. Posttraumatic administration of a sub-anesthetic dose of ketamine exerts neuroprotection via attenuating inflammation and autophagy[J]. Neuroscience, 2017, 343: 30-38.
[13] Engelhard K, Werner C, Eberspächer E, et al. The effect of the α2-agonist dexmedetomidine and the N-methyl-d-aspartate antagonist S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats[J]. Anesth Analg, 2003, 96(2): 524-531.
[14] Lu X, Tang L, Lan H, et al. A comparison of intranasal dexmedetomidine, esketamine or a dexmedetomidine-esketamine combination for induction of anaesthesia in children: a randomized controlled double-blind trial[J]. Front Pharmacol, 2021, 12: 808930.
[15] Xin NX, Xu H, Yue CJ. Comparison between dexmedetomidine and esketamine in pediatric dentistry surgery[J]. Transl Pediatr, 2021, 10(12): 3159-3165.
[16] Wang J, Zeng J, Zhao N, et al. Intranasal esketamine combined with oral midazolam provides adequate sedation for outpatient pediatric dental procedures: a prospective cohort study[J]. Int J Surg, 2023, 109(7): 1893-1899.
[17] Bian Y, Zhou SY, Hou HY, et al. The optimal dose of oral midazolam with or without intranasal S-ketamine for premedication in children: a randomised, double blinded, sequential dose-finding trial[J]. Transl Pediatr, 2021, 10(11): 2941-2951.
[18] Huang JJ, Liu DQ, Bai J, et al. Median effective dose of esketamine for intranasal premedication in children with congenital heart disease[J]. BMC Anesthesiol, 2023, 23(1): 129.
[19] Su M, Zhu YC, Liu SP, et al. Median effective dose (ED50) of esketamine combined with propofol for children to inhibit response of gastroscope insertion[J]. BMC Anesthesiol, 2023, 23(1): 240.
[20] Wang JX, Hu WD, Zhao XL, et al. Sedative effect and safety of different doses of S-ketamine in combination with propofol during gastro-duodenoscopy in school-aged children: a prospective, randomized study[J]. BMC Anesthesiol, 2022, 22(1): 346.
[21] Zheng XS, Huang JJ, Wei SS, et al. Efficacy and safety comparison of esketamine-propofol with nalbuphine-propofol for upper gastrointestinal endoscopy in children: a multi-center randomized controlled trial[J]. Front Pediatr, 2023, 11: 1126522.
[22] Zhong Y, Jiang M, Wang YS, et al. Evaluating efficacy and safety of sub-anesthetic dose esketamine as an adjuvant to propofol/remifentanil analgosedation and spontaneous respiration for children flexible fibreoptic bronchoscopy: a prospective, double-blinded, randomized, and placebo-controlled clinical trial[J]. Front Pharmacol, 2023, 14: 1184663.
[23] Pees C, Haas NA, Ewert P, et al. Comparison of analgesic/sedative effect of racemic ketamine and S(+)-ketamine during cardiac catheterization in newborns and children[J]. Pediatr Cardiol, 2003, 24(5): 424-429.
[24] Eich C, Verhagen-Henning S, Roessler M, et al. Low-dose S-ketamine added to propofol anesthesia for magnetic resonance imaging in children is safe and ensures faster recovery—a prospective evaluation[J]. Paediatr Anaesth, 2011, 21(2): 176-178.
[25] De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation[J]. CNS Neurosci Ther, 2013, 19(6): 403-410.
[26] Choi H, Song JY, Oh EJ, et al. The effect of opioid-free anesthesia on the quality of recovery after gynecological laparoscopy: a prospective randomized controlled trial[J]. J Pain Res, 2022, 15: 2197-2209.
[27] Tu WC, Yuan HB, Zhang SJ, et al. Influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients[J]. Am J Transl Res, 2021, 13(3): 1701-1709.
[28] Liu F, Kong FL, Zhong L, et al. Preoperative esketamine alleviates postoperative pain after endoscopic plasma adenotonsillectomy in children[J]. Clin Med Res, 2023, 21(2): 79-86.
[29] Kim KS, Kwak HJ, Min SK, et al. The effect of ketamine on tracheal intubating conditions without neuromuscular blockade during sevoflurane induction in children[J]. J Anesth, 2011, 25(2): 195-199.
[30] Luo J, Yin KQ, Zhao DH, et al. Effect of intravenous induction with different doses of Esketamine combined with propofol and sufentanil on intraocular pressure among pediatric strabismus surgery: a randomized clinical trial[J]. BMC Anesthesiol, 2023, 23(1): 275.
[31] Patel D, Talbot C, Luo WS, et al. The use of esketamine sedation in the emergency department for manipulation of paediatric forearm fractures: a 5 year study[J]. Injury, 2021, 52(6): 1321-1330.
[32] van de Bunt JA, Veldhoen ES, Nievelstein RAJ, et al. Effects of esketamine sedation compared to morphine analgesia on hydrostatic reduction of intussusception: a case-cohort comparison study[J]. Paediatr Anaesth, 2017, 27(11): 1091-1097.
[33] Chen Y, Ru FX, Ye QP, et al. Effect of S-ketamine administered at the end of anesthesia on emergence delirium in preschool children undergoing tonsillectomy and/or adenoidectomy[J]. Front Pharmacol, 2023, 14: 1044558.
[34] Andolfatto G, Willman E, Joo D, et al. Intranasal ketamine for analgesia in the emergency department: a prospective observational series[J]. Acad Emerg Med, 2013, 20(10): 1050-1054.
[35] Yeaman F, Oakley E, Meek R, et al. Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: a pilot study[J]. Emerg Med Australas, 2013, 25(2): 161-167.
[36] Nemeth M, Jacobsen N, Bantel C, et al. Intranasal analgesia and sedation in pediatric emergency care-a prospective observational study on the implementation of an institutional protocol in a tertiary children's hospital[J]. Pediatr Emerg Care, 2019, 35(2): 89-95.
[37] Qian Q, Liu HX, Li YQ. Effect of esketamine nasal drops on pain in children after tonsillectomy using low temperature plasma ablation[J]. Front Pediatr, 2023, 11: 1110632.
[38] Xu Y, Chen Q, Li P, et al. Safety and efficacy of esketamine for postoperative analgesia in pediatric patients with hypospadias[J]. Front Surg, 2023, 10: 1131137.
[39] Marhofer P, Krenn CG, Plöchl W, et al. S(+)-ketamine for caudal block in paediatric anaesthesia[J]. Br J Anaesth, 2000, 84(3): 341-345.
[40] De Negri P, Ivani G, Visconti C, et al. How to prolong postoperative analgesia after caudal anaesthesia with ropivacaine in children: S-ketamine versus clonidine[J]. Paediatr Anaesth, 2001, 11(6): 679-683.
[41] Hager H, Marhofer P, Sitzwohl C, et al. Caudal clonidine prolongs analgesia from caudal S(+)-ketamine in children[J]. Anesth Analg, 2002, 94(5): 1169-1172

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· 研究进展 ·

艾司氯胺酮在儿童麻醉中的临床应用进展

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摘要：氯胺酮是常用的麻醉药物，但是由于术后噩梦、锥体外系综合征以及滥用倾向等问题，其在 20 世纪 90 年代后期的临床应用有所减少。而艾司氯胺酮作为氯胺酮的异构体，与消旋体氯胺酮相比，应用剂量较小，具有较强的镇痛和镇静作用，心血管和精神方面不良反应小。其代谢快，在体内清除率高，对患儿呼吸循环影响轻微，苏醒和恢复迅速，在小儿麻醉效果方面有显著的应用价值。

关键词：艾司氯胺酮；儿童；镇静；诊疗性操作；麻醉诱导；院前急救镇痛；术后镇痛

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Progress in clinical application of esketamine in pediatric anesthesia

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Abstract: Ketamine is a commonly used anesthetic drug, but its clinical use declined in the late 1990s due to its postoperative nightmares, extrapyramidal syndrome, and a tendency to abuse. As an isomer of ketamine, esketamine is applied in a smaller dose than racemic ketamine, with strong analgesic and sedative effects, fewer cardiovascular and psychiatric adverse reactions. It has a significant application value in pediatric anesthesia with fast metabolism and high clearance rate *in vivo*, slight impact on children's respiratory and circulation, and rapid awakening and recovery.

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艾司氯胺酮是一种多靶点药物，与 N-甲基-D-天门冬氨酸(N-melhyl-D-aspartic acid, NMDA)受体、阿片受体、胆碱能受体、单胺受体以及钠离子通道、钙离子通道等相互作用，产生催眠、镇静、镇痛作用。艾司氯胺酮起效快速，效价更高，清除率快，应用剂量较小，对患儿呼吸循环影响轻微，苏醒和恢复迅速，在小儿麻醉方面有显著的应用价值。此外，其神经保护特性、支气管扩张性、抗痛觉过敏等作用为其在临床中的应用提供了更多选择。本文讨论了艾司氯胺酮在药理学和在儿科临床应用方面的适应证，以期为其临床使用提供借鉴和参考。

1　艾司氯胺酮的药理学特性

艾司氯胺酮是氯胺酮的左旋异构体[1]，其平均消除半衰期约为 4 h，分布容积为 5～10 L/kg，主要通过细胞色素 P450(CYP450)代谢，去甲氯胺酮为主要代谢物，约 78%以尿液形式排出。艾司氯胺酮静脉注射30 s 内起效，1～2 min 即可达到最大血药浓度，作用持续 30～45 min；可以通过肌内注射、口服、滴鼻等多种途径给药。肌内、口服、鼻内给药的生物利用度分别为 93%、16%～24%和 45%～50%。氯胺酮的清除率为 14.8 mg/(kg·min)，而艾司氯胺酮的清除率为 26.3 mg/(kg·min)，艾司氯胺酮代谢产物血浆清除更快，单次静脉给药后苏醒更快。因此，在麻醉和围术期镇痛中采用艾司氯胺酮更可控，患者苏醒快而舒适。艾司氯胺酮产生的意识消失和镇痛作用是剂量相关的，其发挥镇痛作用的血药浓度远低于意识消失所需要的浓度，儿童全身麻醉所需的最低血药浓度为 0.4～2.0 mg/L，但血药浓度≥0.05 mg/L 即可提高痛阈。

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因此在麻醉效应消退后，镇痛效应仍可持续一段时间。

1.1　对 NMDA 受体的作用　氯胺酮包含 S(+)氯胺酮和 R(-)氯胺酮两种立体异构体，可以非竞争性拮抗中枢神经系统中的 NMDA 上的苯环己哌啶(PCP)结合位点[2]。与R(-)异构体相比，艾司氯胺酮对 NMDA 受体的 PCP 位点的亲和力/效力大约高 4 倍，是外消旋混合物的 2 倍。NMDA 受体是一种由两个 GluN1 和两个 GluN2 亚基组成的离子型谷氨酸受体，广泛表达于脑、脊髓、背根神经节等疼痛转导通路中，其激活参与了疼痛传递过程。艾司氯胺酮既可以作为受体通道阻滞剂(有效缩短打开时间)，也可以作为变构调节剂，降低通道打开的频率。其可缓慢地从受体中解离(即使在谷氨酸解离之后)，从而导致持续的封锁，延长通道阻滞时间。疼痛刺激可导致脊髓后角疼痛传导 C 类纤维的敏感突触的持续过度激活，导致大量钙离子进入神经元，激活蛋白激酶 C(PKC)，从而引起 NMDA 受体的磷酸化[3]。抑制 NMDA 受体能直接阻断疼痛的传递途径，减少钙离子内流，直接阻断疼痛的传递途径。

NMDA 受体的激活参与了脊髓高兴奋性和持续性疼痛的发展[4]。艾司氯胺酮可有效防止疼痛刺激引起的长时程增强作用(long-term potentiation, LTP)的发展。除了磷酸化 NMDA 受体外，PKC 可能通过参与与突触后密度(PSD)和细胞骨架蛋白的相互作用，特别是 PSD-95 来调节 NMDA 受体的功能，它与 NMDA 受体相互作用，可能参与脊髓伤害性信号的加工[5]。艾司氯胺酮可以阻断 NMDA 受体和上述病理改变，降低中枢神经系统致敏反应，防止急性疼痛转成慢性和疼痛记忆出现。

1.2　对阿片类受体的作用　艾司氯胺酮对 μ 和 κ 受体的结合力为 R(-)氯胺酮的 2~4 倍[6]。纳洛酮是一种 μ 受体特异性拮抗剂，对 δ 和 κ 受体的作用较弱，大剂量使用纳洛酮时，只能部分拮抗氯胺酮的镇痛作用。氯胺酮引起幻觉的机制可能是通过 κ 受体产生的。阿片类药物可通过激活 μ 受体促进 NMDA 受体的兴奋性，诱发与 LTP 相关的痛觉过敏。艾司氯胺酮可改善 μ 受体功能，在使用阿片类药物之前注射低剂量艾司氯胺酮能预防痛觉过敏。

1.3　对胆碱能和肾上腺素能受体的作用　艾司氯胺酮对 M 胆碱能受体的亲和力是 R(-)氯胺酮的 3 倍。艾司氯胺酮可抑制多巴胺和 5-羟色胺的再摄取，可能会增强中枢多巴胺能神经元的活动。艾司氯胺酮可引起儿茶酚胺释放，抑制去甲肾上腺素重摄取，激活交感神经系统而产生间接的心血管刺激作用，导致血压升高、心率加快，增强儿茶酚胺对支气管平滑肌的舒张作用，对于反应性气道疾病或支气管痉挛的患者，可改善其肺顺应性。艾司氯胺酮通过加强单胺能系统或直接激活相应的脑区来激活下行疼痛抑制通路来缓解疼痛。低剂量艾司氯胺酮可以激活健康志愿者下行抑制通路区域如前扣带皮质、脑岛、前额叶皮质和脑干，其变化与疼痛评分一致。用 α2-肾上腺素受体拮抗剂或 5-羟色胺能受体拮抗剂预处理可完全逆转氯胺酮的镇痛作用[7-8]。其镇静和镇痛作用可能与胆碱能和单胺能系统的正负调节有关，导致阿片系统的敏化与内源性镇痛系统的活性增强。

1.4　其他受体　艾司氯胺酮可通过阻滞电压门控性钠离子通道产生局部麻醉作用。艾司氯胺酮可直接拮抗组胺对支气管平滑肌的致痉挛作用及对 L 型钙离子通道的阻滞来舒张气道平滑肌。艾司氯胺酮产生的催眠作用源于其参与、介导的对超极化激活环核苷酸门控阳离子(HCN)通道的阻滞(HCN-1 主要在皮质中表达，通过改变细胞静息电位和膜阻力来影响神经元的兴奋性)[9]。

1.5　神经保护作用　NMDA 受体的激活在导致从缺血到凋亡的病理生理过程中至关重要，拮抗 NMDA 受体抑制钙流入细胞，减少谷氨酸诱发的神经毒性，对神经元具有保护作用。在严重脑外伤患者可发生扩散性皮质去极化(发生率 54%~100%)，这些去极化波以每分钟 2~7 mm 的速度在整个皮质中扩散，使神经血管脱钩，从而导致脑损伤[10]。研究证实艾司氯胺酮可减少扩散去极化过程[11]。其还具有抗炎作用，可以缓解炎性反应引起的神经损伤和组织疼痛，发挥神经保护作用[12]。艾司氯胺酮的神经保护特性可能与对促凋亡蛋白和抗凋亡蛋白之间平衡的超早期调节有关[13]。

2　艾司氯胺酮的临床应用

2.1　镇静中的应用　因害怕医院的环境和手术，过半数的儿童在手术前表现出明显的焦虑，术前镇静很有必要。术前应用右美托咪定 1 μg/kg 联合艾司氯胺酮 0.5 mg/kg 滴鼻的患儿配合麻醉诱导效果更好，镇静起效时间更短、成功率更高(90%)，麻醉后躁动发生率更低[14]。对于门诊行牙科手术的患儿，术前艾司氯胺酮 0.5 mg/kg 滴鼻，相比右美托咪定滴鼻镇静起效时间明显缩短，术中及术后镇痛效果显著，患儿满意度及治疗完成率高[15]。对于口服 0.5 mg/kg 咪达唑仑的患儿，艾司氯胺酮滴鼻液的 95% 药物有效剂量(ED_{95})为 1.99 mg/kg(95% *CI*：1.95 ~ 2.01 mg/kg)，联合治疗不仅提高了患儿镇静的效果，而且没有增加唤醒时间和不良事件的发生率[16]。术前艾司氯胺酮 0.25 mg/kg 滴鼻，可使口服咪达唑仑的 ED_{90}剂量减少了约 45.2%(0.461 ~0.253 mg/kg)，缩短镇静起效时间及术后恢复时间，同时减少了单独使用咪达唑仑时引起副作用的发生率[17]。对于患有先心病的儿童，艾司氯胺酮用于术前镇静时，其滴鼻给药的 ED_{50}为 0.7 mg/kg，镇静起效时间为(16.39±7.24) min，该剂量安全有效[18]。联合艾司氯胺酮与右美托咪定、咪达唑仑等用于儿科急诊的镇静是安全有效的，这种用药方案可以缩短镇静起效的时间，同时减少使用单一镇静剂时可能引起的副作用，提高患儿在诊疗过程中的舒适度和满意度。

2.2　诊疗性操作中的应用　艾司氯胺酮静脉注射 30 s 起效，清除半衰期短，苏醒迅速，对呼吸抑制轻微，内在拟交感神经活性弱，精神症状副作用少，适用于各种临床诊疗性操作。在小儿无痛上消化道胃镜检查中，小剂量的艾司氯胺酮[ED_{50} 0.143 mg/kg (95% *CI*：0.047 ~ 0.398 mg/kg)]联合丙泊酚(3 mg/kg)具有满意的镇静效果，其安全性和可行性均表现良好[19]。当使用艾司氯胺酮 0.7 mg/kg 联合丙泊酚 3 mg/kg 时，

可以增强学龄儿童在内镜插入时的耐受性(首次插入内镜顺利放置率 83.30%),保持儿童的血流动力学稳定,减少丙泊酚的追加使用次数和丙泊酚的总用量,内镜医师的满意度更高[20]。一项共纳入 200 名患儿的多中心研究发现,艾司氯胺酮组(艾司氯胺酮 0.5 mg/kg、丙泊酚 2 mg/kg)与纳布啡组(纳布啡 0.2 mg/kg、丙泊酚 2 mg/kg)相比,其首次置入内镜的成功率高于纳布啡组(97% *vs* 66%, $P<0.01$)[21]。对于接受柔性纤维支气管镜检查(FFB)检查的患儿,Zhong 等[22]发现亚麻醉剂量(0.3 mg/kg)的艾司氯胺酮与丙泊酚/瑞芬太尼联合使用与丙泊酚/瑞芬太尼联合的方法相比,起效时间更快,患儿术中血流动力学更稳定,术后谵妄评分更低。艾司氯胺酮组麻醉诱导过程中丙泊酚注射引起的疼痛发生率显著降低。艾司氯胺酮与咪达唑仑联合应用可为行心脏导管术的儿童提供不需要插管的深度清醒镇静[23]。与单用丙泊酚相比,艾司氯胺酮联合丙泊酚用于小儿 MRI 检查的恢复速度更快,苏醒质量更好[24]。艾司氯胺酮与其他镇静药物复合使用,有助于提高诊疗操作的成功率,稳定血流动力学,提高中深度镇静和麻醉的安全性及术后恢复质量。

2.3　*术前及麻醉中的应用*　NMDA 谷氨酰胺能传递系统直接参与炎症级联反应包括周围神经、脊髓致敏、神经胶质激活和背根反射等机制[25]。研究证实术前使用艾司氯胺酮可以通过调节手术引起的急性炎症反应和应激诱导的免疫紊乱,减少术后疼痛和促进身体恢复[26-27]。对于进行腔镜腺扁桃体切除术的儿童,与使用芬太尼诱导麻醉组相比,术前使用艾司氯胺酮(1 mg/kg)诱导麻醉组在手术后 c-fos mRNA 和 c-jun mRNA 水平以及面部、腿部、活动、哭泣和安慰(FLACC)评分均显著降低[28]。Fos 和 Jun 蛋白可以敏感而定量地反映应激水平。艾司氯胺酮术前使用可以改善术后应激反应及疼痛。0.5 mg/kg 氯胺酮、5%七氟醚和阿芬太尼 10 μg/kg 的麻醉诱导方案可改善儿童的插管条件,同时保持自主呼吸和血流动力学的稳定性[29]。在 7 ~ 12 岁的儿童患者以不超过 0.5 mg/kg的艾司氯胺酮剂量与丙泊酚和舒芬太尼联合使用,与诱导前状态比较不会升高眼内压(IOP)[30]。这种药物联合方案可抑制喉罩插入引起的 IOP 升高。艾司氯胺酮作为小儿前臂骨折术中用药时,其在镇静镇痛的效果与使用笑气联合鼻内吗啡的效果相当[31]。研究发现与吗啡相比,术中使用艾司氯胺酮进行回肠肠套叠液体静压复位术的患儿,手术成功率更高、复发率更低、同时苏醒时间和住院时间也得以缩短[32]。在麻醉结束时给予艾司氯胺酮(0.2 mg/kg)可有效降低接受扁桃体切除术和/或腺样体切除术的学龄前儿童谵妄的发生率和严重程度,且不会延长拔管时间或增加不良事件[33]。使用艾司氯胺酮具有较高的安全性和有效性,对患儿术后康复具有积极的影响。因此,推荐在临床实践中考虑使用艾司氯胺酮作为麻醉管理的一种选择。

2.4　*院前急救镇痛*　在院前急救过程中出现急性创伤性疼痛(如骨折、烧伤、烫伤)需要治疗或诊断的儿童需要快速有效的镇痛。88%的急诊科患儿鼻内滴注氯胺酮可将 VAS 疼痛评分降低到具有临床意义的程度[34]。鼻内滴注 1.0 mg/kg 氯胺酮可为 3~13 岁中度至重度(VAS≥6/10)疼痛的急诊科儿童提供 30 min 的有效镇痛,患者满意度高,不良反应轻微且呈一过性[35]。4 个月至 16 岁的儿童使用艾司氯胺酮(4 mg/kg)联合咪达唑仑雾化吸入可以快速缓解疼痛、改善患儿焦虑、提高合作率,即使在重复给药后也未观察到呼吸、循环抑制或过度镇静[36]。在静脉通路难以建立的情况下,鼻内艾司氯胺酮给药是一种可靠、微创的给药途径,可对急诊科患者提供有效、快速的镇痛作用。

2.5　*术后镇痛*　扁桃体切除术后儿童使用艾司氯胺酮滴鼻剂可改善疼痛症状,缩短恢复时间及假膜的形成与脱落时间[37]。一项前瞻性、随机、双盲针对 1~5 岁烧伤面积高达全身表面积 10%患儿的研究,结果表明口服咪达唑仑和氯胺酮可提供良好的镇痛效果。接受尿道下裂修复术的患儿术后持续静脉输注艾司氯胺酮[初始剂量为艾司氯胺酮 0.3 mg/kg,维持剂量为艾司氯胺酮 0.15 mg/(kg · h),联合氟比洛芬酯 5 mg/kg]可提供有效镇痛,且低血压和呼吸抑制的发生率明显降低,首次排便时间明显缩短[38]。艾司氯胺酮可通过多种途径为患儿术后提供安全有效的镇痛作用,减少术后不良反应,加速术后恢复,为儿童术后多模式镇痛提供了新的临床思路。

2.6　*椎管内应用*　艾司氯胺酮不含有防腐剂,可以单独或与其他局部麻醉药复合用于椎管内麻醉。给予相同剂量艾司氯胺酮,骶管给药比肌内注射镇痛时间更长。行小儿腹股沟疝修补术时,经骶管内注射艾司氯胺酮 1 mg/kg 可维持镇痛时间 8.8 h,单独使用艾司氯胺酮在术中术后与 0.25%布比卡因(0.75 mg/kg)的镇痛等效[39]。将艾司氯胺酮(0.5 mg/kg)和 0.2%罗哌卡因(2 μg/kg)联用于骶管麻醉可维持约 12 h 的术后镇痛作用,且无明显副作用[40]。1.0 mg/kg 艾司氯胺酮联合 1.0 或 2.0 μg/kg 可乐定骶管阻滞可为儿童提供 24 h 的围手术期镇痛,且副作用极小[41]。

3　结　语

艾司氯胺酮作为唯一可保持自主呼吸具有镇静镇痛作用的静脉麻醉药,在小儿镇静、麻醉应用、急救疼痛管理等方面具有较大价值。艾司氯胺酮因其给药途径多样,可控性强,副作用少等优势可广泛应用于小儿临床。未来可进行多中心临床随机对照研究完善艾司氯胺酮在更多领域的应用,为广大患儿的个性化药物治疗方案提供新思路。

利益冲突　无

参考文献

[1]　龚晓毅,翁立阳,郭冬冬,等.小剂量艾司氯胺酮对无痛胃肠镜检查时丙泊酚联合瑞芬太尼麻醉效果的影响[J].中国临床研究,2022,35(1):61-65.
Gong XY, Weng LY, Guo DD, et al. Effect of low-dose esketamine on intravenous anesthesia of propofol combined with remifentanil during painless gastroenteroscopy[J]. Chin J Clin Res, 2022, 35(1): 61-65.

[2] Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors[J]. Anesthesiology, 1997, 86(4): 903-917.

[3] Benrath J, Brechtel C, Stark J, et al. Low dose of S(+)-ketamine prevents long-term potentiation in pain pathways under strong opioid analgesia in the rat spinal cord *in vivo*[J]. Br J Anaesth, 2005, 95(4): 518-523.

[4] 赵若林,梁丽丽,王冬梅,等.围手术期应用小剂量艾司氯胺酮对胸腔镜肺癌根治术患者术后镇痛的影响[J].中华实用诊断与治疗杂志,2023,37(3):269-272.
Zhao RL, Liang LL, Wang LM, et al. Efficacy of low-dose esketamine on postoperative analgesia in patients undergoing thoracoscopic radical resection of lung cancer[J]. J Clin Pract Diagn Ther, 2023, 37(3): 269-272.

[5] Tao YX, Huang YZ, Mei L, et al. Expression of PSD-95/SAP90 is critical for N-methyl-D-aspartate receptor-mediated thermal hyperalgesia in the spinal cord[J]. Neuroscience, 2000, 98(2): 201-206.

[6] Hirota K, Okawa H, Appadu BL, et al. Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells[J]. Anesthesiology, 1999, 90(1): 174-182.

[7] Koizuka S, Obata H, Sasaki M, et al. Systemic ketamine inhibits hypersensitivity after surgery via descending inhibitory pathways in rats[J]. Can J Anaesth, 2005, 52(5): 498-505.

[8] Niesters M, Khalili-Mahani N, Martini C, et al. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers[J]. Anesthesiology, 2012, 117(4): 868-877.

[9] Zhou C, Douglas JE, Kumar NN, et al. Forebrain HCN1 channels contribute to hypnotic actions of ketamine[J]. Anesthesiology, 2013, 118(4): 785-795.

[10] Dreier JP, Fabricius M, Ayata C, et al. Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group[J]. J Cereb Blood Flow Metab, 2017, 37(5): 1595-1625.

[11] Hertle DN, Dreier JP, Woitzik J, et al. Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury[J]. Brain, 2012, 135(Pt 8): 2390-2398.

[12] Wang CQ, Ye Y, Chen F, et al. Posttraumatic administration of a sub-anesthetic dose of ketamine exerts neuroprotection via attenuating inflammation and autophagy[J]. Neuroscience, 2017, 343: 30-38.

[13] Engelhard K, Werner C, Eberspächer E, et al. The effect of the α2-agonist dexmedetomidine and the N-methyl-d-aspartate antagonist S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats[J]. Anesth Analg, 2003, 96(2): 524-531.

[14] Lu X, Tang L, Lan H, et al. A comparison of intranasal dexmedetomidine, esketamine or a dexmedetomidine-esketamine combination for induction of anaesthesia in children: a randomized controlled double-blind trial[J]. Front Pharmacol, 2021, 12: 808930.

[15] Xin NX, Xu H, Yue CJ. Comparison between dexmedetomidine and esketamine in pediatric dentistry surgery[J]. Transl Pediatr, 2021, 10(12): 3159-3165.

[16] Wang J, Zeng J, Zhao N, et al. Intranasal esketamine combined with oral midazolam provides adequate sedation for outpatient pediatric dental procedures: a prospective cohort study[J]. Int J Surg, 2023, 109(7): 1893-1899.

[17] Bian Y, Zhou SY, Hou HY, et al. The optimal dose of oral midazolam with or without intranasal S-ketamine for premedication in children: a randomised, double blinded, sequential dose-finding trial[J]. Transl Pediatr, 2021, 10(11): 2941-2951.

[18] Huang JJ, Liu DQ, Bai J, et al. Median effective dose of esketamine for intranasal premedication in children with congenital heart disease[J]. BMC Anesthesiol, 2023, 23(1): 129.

[19] Su M, Zhu YC, Liu SP, et al. Median effective dose (ED_{50}) of esketamine combined with propofol for children to inhibit response of gastroscope insertion[J]. BMC Anesthesiol, 2023, 23(1): 240.

[20] Wang JX, Hu WD, Zhao XL, et al. Sedative effect and safety of different doses of S-ketamine in combination with propofol during gastro-duodenoscopy in school-aged children: a prospective, randomized study[J]. BMC Anesthesiol, 2022, 22(1): 346.

[21] Zheng XS, Huang JJ, Wei SS, et al. Efficacy and safety comparison of esketamine-propofol with nalbuphine-propofol for upper gastrointestinal endoscopy in children: a multi-center randomized controlled trial[J]. Front Pediatr, 2023, 11: 1126522.

[22] Zhong Y, Jiang M, Wang YS, et al. Evaluating efficacy and safety of sub-anesthetic dose esketamine as an adjuvant to propofol/remifentanil analgosedation and spontaneous respiration for children flexible fibreoptic bronchoscopy: a prospective, double-blinded, randomized, and placebo-controlled clinical trial[J]. Front Pharmacol, 2023, 14: 1184663.

[23] Pees C, Haas NA, Ewert P, et al. Comparison of analgesic/sedative effect of racemic ketamine and S(+)-ketamine during cardiac catheterization in newborns and children[J]. Pediatr Cardiol, 2003, 24(5): 424-429.

[24] Eich C, Verhagen-Henning S, Roessler M, et al. Low-dose S-ketamine added to propofol anesthesia for magnetic resonance imaging in children is safe and ensures faster recovery—a prospective evaluation[J]. Paediatr Anaesth, 2011, 21(2): 176-178.

[25] De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation[J]. CNS Neurosci Ther, 2013, 19(6): 403-410.

[26] Choi H, Song JY, Oh EJ, et al. The effect of opioid-free anesthesia on the quality of recovery after gynecological laparoscopy: a prospective randomized controlled trial[J]. J Pain Res, 2022, 15: 2197-2209.

[27] Tu WC, Yuan HB, Zhang SJ, et al. Influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients[J]. Am J Transl Res, 2021, 13(3): 1701-1709.

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镜肺癌根治术患者的麻醉效果和术后镇痛效果[J].癌症进展,2021,19(10):1019-1022.
Li JS, An J, Song HW, et al. Anesthesia and postoperative analgesic effects of general anesthesia combined with thoracic paravertebral block in patients undergoing thoracoscopic radical resection of lung cancer[J]. Oncol Prog, 2021, 19(10): 1019-1022.

[14] 郭延洪,阿良德,李孔兵,等.超声引导肋间神经阻滞与多次注射胸椎旁阻滞对老年胸腔镜手术患者术后镇痛效果的影响[J].中国老年学杂志,2022,42(22):5498-5501.
Guo YH, E LD, Li KB, et al. Effects of ultrasound-guided intercostal nerve block and multiple injections of thoracic paravertebral block on postoperative analgesia in elderly patients undergoing thoracoscopic surgery[J]. Chin J Gerontol, 2022, 42(22): 5498-5501.

[15] 王辰.超声引导椎旁神经阻滞与肋间神经阻滞在电视胸腔镜手术术后疼痛控制中前瞻性随机对照研究[J].生物医学工程与临床,2020,24(2):144-147.
Wang C. Prospective randomized controlled study of ultrasound-guided paravertebral nerve block and intercostal nerve block in pain control after video-assisted thoracoscopic surgery[J]. Biomed Eng Clin Med, 2020, 24(2): 144-147.

[16] Chen N, Qiao Q, Chen RM, et al. The effect of ultrasound-guided intercostal nerve block, single-injection erector spinae plane block and multiple-injection paravertebral block on postoperative analgesia in thoracoscopic surgery: a randomized, double-blinded, clinical trial[J]. J Clin Anesth, 2020, 59: 106-111.

[17] 王锋锋,王展,徐志云.超声引导下胸椎旁神经阻滞和肋间神经阻滞的应用比较[J].南通大学学报(医学版),2022,42(3):244-247.
Wang FF, Wang Z, Xu ZY. Comparison of ultrasound-guided thoracic paravertebral nerve block and intercostal nerve block[J]. J Nantong Univ Med Sci, 2022, 42(3): 244-247.

[18] 张冉,霍飞,田龙,等.超声引导下椎旁神经阻滞与肋间神经阻滞用于胸腔镜肺部术后镇痛效果的比较[J].临床麻醉学杂志,2020,36(9):886-889.
Zhang R, Huo F, Tian L, et al. Comparison of analgesic effect of ultrasound-guided paravertebral block and intercostal nerve block after thoracoscopic pulmonary surgery[J]. J Clin Anesthesiol, 2020, 36(9): 886-889.

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(上接第 509 页)

[28] Liu F, Kong FL, Zhong L, et al. Preoperative esketamine alleviates postoperative pain after endoscopic plasma adenotonsillectomy in children[J]. Clin Med Res, 2023, 21(2): 79-86.

[29] Kim KS, Kwak HJ, Min SK, et al. The effect of ketamine on tracheal intubating conditions without neuromuscular blockade during sevoflurane induction in children[J]. J Anesth, 2011, 25(2): 195-199.

[30] Luo J, Yin KQ, Zhao DH, et al. Effect of intravenous induction with different doses of Esketamine combined with propofol and sufentanil on intraocular pressure among pediatric strabismus surgery: a randomized clinical trial[J]. BMC Anesthesiol, 2023, 23(1): 275.

[31] Patel D, Talbot C, Luo WS, et al. The use of esketamine sedation in the emergency department for manipulation of paediatric forearm fractures: a 5 year study[J]. Injury, 2021, 52(6): 1321-1330.

[32] van de Bunt JA, Veldhoen ES, Nievelstein RAJ, et al. Effects of esketamine sedation compared to morphine analgesia on hydrostatic reduction of intussusception: a case-cohort comparison study[J]. Paediatr Anaesth, 2017, 27(11): 1091-1097.

[33] Chen Y, Ru FX, Ye QP, et al. Effect of S-ketamine administered at the end of anesthesia on emergence delirium in preschool children undergoing tonsillectomy and/or adenoidectomy[J]. Front Pharmacol, 2023, 14: 1044558.

[34] Andolfatto G, Willman E, Joo D, et al. Intranasal ketamine for analgesia in the emergency department: a prospective observational series[J]. Acad Emerg Med, 2013, 20(10): 1050-1054.

[35] Yeaman F, Oakley E, Meek R, et al. Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: a pilot study[J]. Emerg Med Australas, 2013, 25(2): 161-167.

[36] Nemeth M, Jacobsen N, Bantel C, et al. Intranasal analgesia and sedation in pediatric emergency care-a prospective observational study on the implementation of an institutional protocol in a tertiary children's hospital[J]. Pediatr Emerg Care, 2019, 35(2): 89-95.

[37] Qian Q, Liu HX, Li YQ. Effect of esketamine nasal drops on pain in children after tonsillectomy using low temperature plasma ablation[J]. Front Pediatr, 2023, 11: 1110632.

[38] Xu Y, Chen Q, Li P, et al. Safety and efficacy of esketamine for postoperative analgesia in pediatric patients with hypospadias[J]. Front Surg, 2023, 10: 1131137.

[39] Marhofer P, Krenn CG, Plöchl W, et al. S(+)-ketamine for caudal block in paediatric anaesthesia[J]. Br J Anaesth, 2000, 84(3): 341-345.

[40] De Negri P, Ivani G, Visconti C, et al. How to prolong postoperative analgesia after caudal anaesthesia with ropivacaine in children: S-ketamine versus clonidine[J]. Paediatr Anaesth, 2001, 11(6): 679-683.

[41] Hager H, Marhofer P, Sitzwohl C, et al. Caudal clonidine prolongs analgesia from caudal S(+)-ketamine in children[J]. Anesth Analg, 2002, 94(5): 1169-1172.

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