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Progress in clinical application of ketamine combined with other anesthetic drugs

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Abstract: Esketamine is an N-methyl-D-aspartic acid (NMDA) receptor antagonist, which has a better effect than ketamine in anesthesia. Esketamine can act on the nervous system, respiratory system, circulatory system, etc. Due to its fast onset and rapid metabolism, it has unique advantages in anesthesia management. Esketamine can not only be used alone in short-term anesthesia operations, but also in combination with various anesthetic drugs, providing a new choice for anesthesia management. Esketamine can not only be used alone in short-term anesthesia operations, but also in combination with various anesthetic drugs, providing a new choice for anesthesia management in various clinical surgeries and outpatient examinations.

Keywords: Esketamine; Ketamine; Anesthesia; Propofol; Midazolam; Analgesia

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Ketamine is an intravenous anesthetic drug with both analgesic and sedative effects and is widely used in clinical anesthesia and sedation[1]. Esketamine, the dextro isomer of ketamine, was initially used as a psychotropic drug to suppress central nervous system excitability, thereby exerting an antidepressant effect, which can help to improve cognitive and neurological functioning and alleviate depressive symptoms in patients[2]. In recent years, esketamine has been found to have fewer side effects and more sedative activity than ketamine, and is therefore being used in a variety of clinical procedures and outpatient examinations. Esketamine has high affinity with N-methyl-D-aspartic acid (NMDA) receptors, which can reduce the dosage of intravenous or inhalation anesthetics, and it has potential neuroprotective effects, avoiding nociceptive sensitization, preventing postoperative delirium, and decreasing postoperative cognitive dysfunction[3]. With the development of medical technology, the increase of surgical complexity and the growth of the number of critical patients, how to choose the appropriate anesthetic sedation plan according to different surgical requirements and the patient's own situation has become one of the important challenges faced by anesthesiologists nowadays[4]. Although esketamine's has a broad prospect in clinical application, its entry into the domestic market is relatively short. In view of this, the present study is intended to review the clinical application of esketamine and its combination with other anesthesia drugs, with the aim of providing ideas for the application of esketamine and the optimization of the selection of clinical anesthesia drugs for surgical procedures.

1 Overview of esketamine

Esketamine is a white or almost white crystalline powder that is both water-soluble and fat-soluble. Esketamine can be administered in various ways, including intravenously, nasally, subcutaneously, intramuscularly, and rectally. In addition, esketamine is mainly excreted through the kidneys, and compared with ketamine, its clearance is significantly increased. Its plasma concentration will rapidly decrease within 2-4 hours after administration, so the respiratory depression of patients with esketamine is milder, and it has less effect on the circulation, and fewer postoperative adverse reactions[5-6].

Esketamine has the same target as ketamine, i.e. NMDA receptor. In addition, esketamine also affects the opioid receptors, monoaminergic and cholinergic receptors, gamma-aminobutyric acid (GABA) receptor, etc. NMDA receptor is widely distributed in the brain, and plays an important role in neuronal development and differentiation. NMDA receptors are widely distributed in the brain and play an essential role in neuronal development and differentiation. Studies have shown that the activation of NMDA receptors is one of the primary mechanisms that trigger nociceptive sensitization. As a receptor antagonist of NMDA, esketamine can be involved in the regulation of synaptic transmission by inhibiting the activity of the NMDA receptor channel, which in turn reduces the release of glutamate, regulates central sensitization, produces general anesthesia, and prevents pain from turning into chronic pain[7]. It has been reported that esketamine also has a high affinity for opioid receptors and can exert its analgesic effect through agonism with opioid receptors, with the primary mechanism of action being binding to μ- and δ-receptors, thereby reducing the use of anesthetic drugs[8]. Therefore, in some studies, esketamine is often used in combination with other anesthetic drugs in surgical anesthesia to reduce the respiratory depression caused by opioids and high-dose sedative drugs and to improve the quality of postoperative recovery[9]. Esketamine can also inhibit the local absorption and reuptake of monoamine

neurotransmitter catecholamines, resulting in a significant accumulation of catecholamines, promoting the body to play a sympathomimetic role in the hyperadrenergic state, thus achieving the effect of bronchodilatation and vasodilatation of vascular smooth muscle[10].

Regarding cholinergic receptors, some researchers have found that esketamine can block neuromuscular junction transmission through nicotinic and muscarinic receptors mediating excitatory effects in the central nervous system[11]. GABA neurons are widely distributed in the central nervous system, and most play an inhibitory role as intermediate neurons. Some studies have demonstrated that esketamine does not have a strong affinity for GABA at subanesthetic doses, but stimulates GABA receptors in the spinal cord at higher concentrations, thereby affecting the release of excitatory and inhibitory transmitters from neurons[12]. It is evident that esketamine can mediate local anesthetic effects in various forms and has excellent pharmacological and clinical value.

2 Clinical use of esketamine

2.1 Individual administration

The pharmacological characteristics of esketamine allow for various application scenarios, and a single administration of esketamine is often applied in short procedures, pre-hospital emergencies, disaster medicine, and diagnostic operations. For short procedures and painless diagnosis and treatment, intravenous injection of 0.5-1.0 mg/kg esketamine is usually sufficient to achieve good sedation and analgesia. Zhan et al.[13] pointed out that, compared with propofol alone, the choice of esketamine as an anesthesia drug also meets the needs of endoscopy, and it can better maintain the hemodynamic stability of the patient and reduce the incidence of adverse effects. Hublet et al.[14] compared the anesthesia effect of esketamine with sufentanil and came to a similar conclusion that esketamine anesthesia can provide effective sedation and analgesia. At the same time, it can effectively reduce the incidence of somatic reactions and improve the quality of patients' early postoperative recovery. In pre-hospital emergency and disaster medicine, esketamine's good stability and long-term validity make it more advantageous when dealing with emergencies. It has been found that esketamine has sympathomimetic effects, and its application to patients with severe craniocerebral injuries will not increase their intracranial pressure. It can protect the nerves and help patients maintain spontaneous respiration[15]. In addition, esketamine can be administered in various ways and is highly controllable. As children are less mature and less cooperative than adult patients, pediatric emergency physicians can administer esketamine orally, nasally, or intramuscularly, which is more acceptable to children. Furthermore, esketamine is safer than opioids, requires lower doses, has a faster onset of action, has fewer side effects on children, and significantly reduces the incidence of agitation after anesthesia[16]. Thus, the single use of esketamine has certain feasibility in clinical anesthesia, and the reasonable application of esketamine in specific scenarios can achieve the same analgesic and sedative effects as opioids, creating a safe and comfortable anesthetic choice for more patients.

2.2 Combined administration

2.2.1 Propofol

Propofol is a kind of intravenous anesthetic with extensive clinical applications. It is commonly used in the induction and maintenance of general anesthesia by inhibiting NMDA receptors and agonist GABA receptors to play the role of anesthesia. Although propofol has a rapid onset of action, stable blood concentration, and rapid awakening, some studies have also pointed out[17] that propofol has a certain degree of neurotoxicity, which may affect the cognitive function of patients. The combined use of esketamine and propofol is an emerging combined anesthesia method that can complement each other's weaknesses in recent years. Wang et al.[18] showed that, compared with the single use of propofol, esketamine combined with propofol in hysteroscopic anesthesia has less impact on the patient's circulatory and respiratory system, and also reduces the amount of perioperative propofol, shortens the patient's postoperative recovery time, and reduces adverse effects such as respiratory depression, bradycardia, and pain at the injection site. In a study of general anesthesia, researchers found that esketamine combined with propofol can stabilize cerebral blood flow rate and reduce the incidence of postoperative cognitive dysfunction in patients, which may be related to the neuroprotective effect of esketamine[19]. Chen et al.[20] also showed that compared with other drugs combined with propofol, esketamine has irreplaceable advantages, and its sympathomimetic and analgesic effects can effectively improve the injection pain and pain caused by propofol. Its sympathomimetic and analgesic effects can effectively improve the injection pain caused by propofol and the inhibitory effect on the cardiovascular system, which in turn can reduce the side effects of propofol. At the same time, some researchers also pointed out that one of the side effects of esketamine, neuropsychiatric reactions during awakening, can also be improved by combining with propofol, which may be related to the ability of propofol to reduce cerebral blood flow and intracranial pressure in patients[21].

2.2.2 Dexmedetomidine

Dexmedetomidine is a kind of α2-adrenoceptor agonist that does not cause respiratory depression and has a better sedative effect. However, it can not be used alone for induction and maintenance of general anesthesia, so it is often used in combination with other anesthetic drugs in clinics. Studies have shown that dexmedetomidine combined with esketamine has higher safety, especially in the surgical treatment of children, the combination can

obtain higher sedation and hemodynamic stability, and does not increase the incidence of adverse reactions[22]. Dexmedetomidine combined with esketamine also achieved better results in the anesthesia management of the elderly group, Ren *et al.*[23] showed in a study on the implementation of stabilized analgesic anesthesia in elderly patients that the application of a small dose of esketamine combined with dexmedetomidine could meet the safe needs, with less impact on the patient's postoperative recovery, and avoid the cardiovascular reaction and immunosuppression caused by opioids, in turn reducing the difficulty and risk of anesthesia management in elderly patients. In other types of anesthesia scenarios, dexmedetomidine combined with esketamine can also improve the quality of patients' postoperative recovery and reduce the level of postoperative pain. For example, in an anesthesia study on patients with breast cancer, dexmedetomidine in combination with esketamine not only reduced postoperative inflammatory response and nerve damage, but also controlled pain and reduced patients' need for opioids, thereby improving the quality of patients' postoperative recovery [24]. A study of laparoscopic gallbladder surgery also showed that dexmedetomidine combined with esketamine improved the quality of surgery, relieved postoperative agitation, and accelerated the recovery of the patient's cognitive function, which is related to the fact that esketamine can directly inhibit the stress response through the stimulation of the sympathetic nervous system[25]. Thus, dexmedetomidine combined with esketamine can be applied to anesthesia management with certain safety and efficacy.

2.2.3 Midazolam

Midazolam is a powerful sedative that can be taken orally, with nasal drip, intramuscular injection, and intravenous injection, with fast onset of action, few side effects, and fast excretion. In patients with brain injury, anesthesia with midazolam in combination with esketamine can regulate perioperative inflammatory response and improve intracranial pressure, thus avoiding the occurrence of postoperative agitation, hypotension and other adverse reactions[26]. Ou *et al.*[27] pointed out that midazolam combined with esketamine can complement each other's strengths and produce an ideal sedative effect, which can effectively reduce the abnormal sympathetic excitation of elderly patients with lower limb fracture, help to stabilize the patient's hemodynamics, reduce the secretion of adrenocorticotropic hormone, and alleviate the patient's stress response to the surgery. Wang *et al.*[28] found that using intranasal esketamine in conjunction with oral midazolam for noninvasive anesthesia had a higher success rate and better sedation effect than an intravenous injection, which could alleviate the children's fear and anxiety of dental treatment and improve their degree of cooperation. Zhou *et al.*[29] also found in another study of extremity resection in children that esketamine nasal drops combined with oral midazolam had a faster onset of action and postoperative recovery, and that the synergistic effect of the drugs could be achieved by reducing the dose of the two drugs alone, thus decreasing the likelihood of multiple adverse effects.

2.2.4 Ropivacaine

Ropivacaine is a long-acting local anesthetic with low toxicity, commonly used in epidural block anesthesia, and its combined use with other anesthetic drugs can help prolong the duration of anesthesia and reduce the use of postoperative analgesics. The combination of ropivacaine and esketamine is commonly used in delivery and some orthopedic surgeries. It has been reported that ropivacaine combined with esketamine not only provides analgesia during delivery, but also improves brain function and significantly reduces the incidence of post-partum depression, which is possibly related to the regulation of serum leptin, norepinephrine, and epinephrine[30]. Guo *et al.*[31] showed that the analgesic effect of ropivacaine combined with esketamine-based block anesthesia in patients undergoing lower extremity fracture surgery was comparable to that of ropivacaine combined with sufentanil, and had better analgesic satisfaction. The incidence of adverse effects was not elevated. A study on the anesthetic management of patients with upper extremity fracture also showed that ropivacaine combined with esketamine for upper brachial plexus block has a better anesthetic effect, which can reduce the incidence of rebound pain after block, increase the safety of the operation, and can also reduce the amount of postoperative sufentanil, which is conducive to the patient's post-operative recovery[32]. Ropivacaine combined with esketamine can also be used in the anesthesia management of fracture surgery in elderly patients. Compared with ropivacaine alone, ropivacaine combined with esketamine will not reduce the scope of the nerve block. It will not affect the recovery of cognitive and neurological functions of the patients, which is safe to a certain extent[33].

2.2.5 Sufentanil

Sufentanil is a kind of strong opioid analgesic, with a better analgesic effect and longer duration of analgesia. However, the application of overdose is easier to cause respiratory inhibition, circulatory inhibition, and other adverse reactions. Sufentanil also has a degree of dependence, so its clinical application is limited. In addition to analgesia, sedation, and anesthesia, esketamine has a preventive effect on opioid-induced nociceptive hypersensitivity, with faster metabolism and awakening, mild neurological adverse reactions, less respiratory secretion, and obvious neuroprotective effects. Yan *et al.*[34] believe that adding esketamine to the application of sufentanil improves the quality and efficacy of anesthesia, reduces the dosage of sufentanil, and thus limits the potential adverse effects of the drug, making its clinical application somewhat limited. Yan et al. concluded that adding esketamine to sufentanil could improve the quality and efficacy of anesthesia, reduce the dosage of sufentanil, and thus limit the potential adverse effects of the drug, making it safer for clinical use. Li *et al.*[35] showed that sufentanil combined with esketamine

in hip arthroplasty could achieve a satisfactory analgesic effect, and at the same time reduce the patient's agitation during the awakening period, which was speculated to be related to the fact that esketamine could reverse the respiratory depression caused by sufentanil by increasing the body's sensitivity to carbon dioxide. In a study on hysteroscopic surgery, researchers found that a subanesthetic dose of esketamine-assisted sufentanil for anesthesia was sufficient to stabilize the patient's blood pressure and heart rate, which reduced postoperative pain and perioperative consumption of sufentanil while improving patient anxiety, which in turn improved patient satisfaction with the treatment[36]. Saugel *et al.*[37] also showed that compared to the use of sufentanil alone, the combined intravenous administration of patients with combined intravenous esketamine had a smoother circulation during general anesthesia and consumed fewer opioids and had significantly lower pain scores postoperatively compared with a single administration of sufentanil. It can be seen that the combination of sufentanil and esketamine is a more efficient drug regimen, which not only provides effective analgesia but also reduces the adverse effects caused by sufentanil and improves the safety of anesthesia.

3 Summary

Due to its advantages of high safety and controllability, esketamine has been used in a variety of surgical scenarios and in combination with a variety of anesthesia drugs to achieve better effects. The incidence of adverse effects of esketamine is related to the dosage used, and the side effects are relatively minor, with elevated heart rate, blood pressure and respiratory depression only in the case of high dosage use. Esketamine not only has strong analgesic and sedative effects, but also improves patients' postoperative cognitive function and negative emotions, which has a broad clinical application prospect. However, esketamine is still a new drug in China, and its clinical application is relatively inexperienced. Therefore, prospective, large-sample experimental studies involving different types of surgeries are still needed to provide patients with safe and comfortable anesthesia options.

Conflict of interest None

Reference

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· 研究进展 ·

艾司氯胺酮联合其他麻醉药物的临床应用进展

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摘要：艾司氯胺酮是一种 N-甲基-D-天冬氨酸（NMDA）受体拮抗剂，较氯胺酮的麻醉镇痛效果更好。艾司氯胺酮可作用于神经系统、呼吸系统、循环系统等，因其起效较快、代谢迅速，在麻醉管理中具有独特的优势。艾司氯胺酮不仅可单独应用于短效麻醉操作中，还可与多种麻醉药物联合应用，为各类临床手术及门诊检查的麻醉管理提供了新的选择。

关键词：艾司氯胺酮；氯胺酮；麻醉；丙泊酚；咪达唑仑；镇痛

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Progress in clinical application of esketamine combined with other anesthetic drugs

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Abstract: Esketamine is an N-methyl-D-aspartic acid (NMDA) receptor antagonist, which has a better effect than ketamine in anesthesia. Esketamine can act on the nervous system, respiratory system, circulatory system, etc. Due to its fast onset and rapid metabolism, it has unique advantages in anesthesia management. Esketamine can not only be used alone in short-term anesthesia operations, but also in combination with various anesthetic drugs, providing a new choice for anesthesia management in various clinical surgeries and outpatient examinations.

Keywords: Esketamine; Ketamine; Anesthesia; Propofol; Midazolam; Analgesia

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氯胺酮是一种兼具镇痛及镇静效果的静脉麻醉药物，被广泛应用于临床麻醉和镇静[1]。艾司氯胺酮是氯胺酮的右旋异构体，最初被用作精神药物，可抑制中枢神经系统的兴奋性，进而发挥抗抑郁作用，能帮助改善患者认知功能及神经功能，减轻患者抑郁症状[2]。近年来，艾司氯胺酮被发现较氯胺酮的副作用更少、镇静活性更强，因此逐渐被应用于各类临床手术和门诊检查中。艾司氯胺酮与 N-甲基-D-天冬氨酸（N-methyl-D-aspartic acid, NMDA）受体的亲和度很高，使用后可减少静脉或吸入麻醉药的用量，且其具有潜在的神经保护作用，可避免痛觉过敏、预防术后谵妄、降低术后认知功能障碍[3]。随着医疗技术的发展，手术复杂性的提高及危重患者数量的增长，如何根据不同手术要求及患者自身情况选择合适的麻醉镇静方案成为了目前麻醉医师面临的重要挑战之一[4]。虽然艾司氯胺酮在临床应用中具有广阔的前景，但其进入国内市场时间较短。鉴于此，本研究拟对艾司氯胺酮及其联合其他麻醉药物的临床应用作一综述，以期为艾司氯胺酮的应用及临床手术麻醉用药的优化选择提供思路。

1　艾司氯胺酮概述

艾司氯胺酮是一种白色或几乎白色的结晶性粉末，兼具水溶性和脂溶性。艾司氯胺酮的给药方式较为多样，可经静脉、鼻腔、皮下、肌肉、直肠等多种方式给药。另外，艾司氯胺酮主要通过肾脏排泄，与氯胺酮相比，其体内清除率也显著增加，在给药后 2~4 h 内其在患者血浆浓度就会迅速下降。因此使用艾司氯胺酮后患者的呼吸抑制较轻，对机体循环影响较小，术后也较少发生不良反应[5-6]。

艾司氯胺酮与氯胺酮具有相同的作用靶点，即 NMDA 受体，除此之外，艾司氯胺酮还对阿片受体、单胺能和胆碱能递质受体、γ-氨基丁酸（gamma-aminobutyric acid, GABA）受体等具有一定作用。NMDA 受体广泛分布于大脑中，在神经元发育、分化中发挥着重要作用。研究显示，NMDA 受体的激活是引发痛觉过敏的主要机制之一，艾司氯胺酮作为 NMDA 的受体拮抗剂，可通过抑制 NMDA 受体通道活性参与调控突触传递，进而降低谷氨酸的释放，调节中枢敏化，产生全身麻醉作

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用并防止疼痛转变为慢性疼痛[7]。据报道,艾司氯胺酮对阿片受体同样具有较高的亲和力,可通过对阿片受体的激动作用发挥镇痛效果,主要作用机制为与 μ 受体和 δ 受体结合从而减少麻醉药物的使用[8]。因此在一些研究中,艾司氯胺酮常与其他麻醉药物联合应用于手术麻醉中,以减轻阿片类药物及大剂量镇静药物引起的呼吸抑制,提高术后恢复质量[9]。艾司氯胺酮还可抑制单胺类神经递质儿茶酚胺的局部吸收及再摄取,导致儿茶酚胺类物质大量积聚,引起机体高肾上腺素能状态发挥拟交感作用,从而达到舒张支气管、舒张血管平滑肌的作用[10]。而关于胆碱能递质受体,一些研究者发现,艾司氯胺酮可通过烟碱和毒蕈碱受体介导中枢神经系统兴奋作用,从而阻遏神经肌肉接头传递[11]。GABA 神经元广泛分布于中枢神经系统中,大部分作为中间神经元发挥抑制作用。一些研究证明,艾司氯胺酮在亚麻醉剂量下对 GABA 不具有很强的亲和力,而在较高浓度下才会刺激脊髓中的 GABA 受体,从而影响神经元兴奋性和抑制性递质的释放[12]。可见,艾司氯胺酮可通过多种形式介导局部麻醉效应,在药理和临床方面的价值等待被挖掘。

2　艾司氯胺酮的临床应用

2.1　单独用药　艾司氯胺酮独特的药理学特点使其的应用场景拥有了多样化的选择,艾司氯胺酮的单一用药常出现在短小手术、院前急救、灾难医学及诊断性操作中。对于短小手术及无痛诊疗,通常静脉注射 0.5~1.0 mg/kg 艾司氯胺酮即可获得较好的镇静镇痛效果。Zhan 等[13]在一项关于无痛胃肠镜的研究中指出,与单一使用丙泊酚相比,选择艾司氯胺酮作为麻醉药物同样能满足内镜检查需要,还可更好地维持患者血流动力学稳定,减少各类不良反应的发生率。Hublet 等[14]比较艾司氯胺酮与舒芬太尼的麻醉效果也得到了类似的结论,应用艾司氯胺酮进行麻醉在提供稳定有效的镇静、镇痛效果的同时,还可有效降低患者体动反应的发生率,改善患者术后早期恢复质量。而在院前急救以及灾难医学方面,艾司氯胺酮所拥有的良好的稳定性和较长的保质期让其在应对紧急事故时更具优势。研究发现,艾司氯胺酮具有拟交感神经效应,重度颅脑损伤患者应用艾司氯胺酮不会升高其颅内压,且可保护神经,帮助患者维持自主呼吸[15]。另外,艾司氯胺酮可通过多种方式给药,可控性较高。儿童机体尚未发育成熟,配合度较成年患者低,儿科急诊医师可通过口服、鼻喷、肌肉注射等多种形式给药,患儿更易接受;并且,艾司氯胺酮较阿片类药物更安全,所需剂量低,起效快,对患儿的副作用小,还可显著降低麻醉后躁动的发生率[16]。由此可见,单一使用艾司氯胺酮方案在临床麻醉中具有一定可行性,在特定的场景中合理应用艾司氯胺酮可达到与阿片类药物相同的镇痛及镇静效果,为更多患者提供安全、舒适的麻醉选择。

2.2　联合用药

2.2.1　丙泊酚　丙泊酚是临床上应用较多的一种静脉麻醉剂,常用于全身麻醉的诱导和维持,主要通过抑制 NMDA 受体及激动 GABA 受体发挥麻醉作用。虽然丙泊酚的起效较快,血药浓度稳定,苏醒迅速,但一些研究也指出,丙泊酚具有一定的神经毒性,可能会影响患者的认知功能[17]。艾司氯胺酮与丙泊酚联合使用是近年来新兴的一种复合麻醉方法,可以扬长补短,互相补充。Wang 等[18]研究显示,与单一使用丙泊酚相比,艾司氯胺酮联合丙泊酚应用于宫腔镜麻醉中对患者的循环和呼吸系统影响更小,还可减少围术期丙泊酚用量,缩短患者术后恢复时间,降低呼吸抑制、心动过缓、注射部位疼痛等不良反应发生率。在一项全身麻醉的研究中,研究者发现,艾司氯胺酮联合丙泊酚可稳定脑血流速度,降低患者术后认知功能障碍的发生率,这可能与艾司氯胺酮的神经保护作用有关[19]。Chen 等[20]研究同样显示,与其他药物联合丙泊酚相比,艾司氯胺酮具有不可替代的优势,其拟交感作用及镇痛作用可有效改善丙泊酚引起的注射疼痛及对心血管系统的抑制作用,进而减轻和补偿丙泊酚的副作用。同时,一些研究者也指出,艾司氯胺酮的副作用之一,觉醒期间的神经精神反应,也可通过与丙泊酚联合应用而得到改善,猜测可能与丙泊酚能降低患者脑血流量、颅内压等有关[21]。

2.2.2　右美托咪定　右美托咪定是一种 α2 肾上腺素受体激动剂,不会引起呼吸抑制,镇静效果较好,但不能单独用于全身麻醉诱导和维持,因此在临床中常与其他麻醉药物联合使用。研究显示,右美托咪定联合艾司氯胺酮具有较高的安全性,特别是在对儿童的手术治疗中,二者联合可获得更高的镇静效果及血流动力学稳定性,且不会增加不良反应的发生率[22]。右美托咪定联合艾司氯胺酮在老年群体的麻醉管理中同样取得了较好的效果,任海强等[23]在一项有关老年患者实施安定镇痛麻醉的研究中显示,应用小剂量艾司氯胺酮联合右美托咪定即可满足安全麻醉需求,对患者术后恢复影响较小,且规避了阿片类药物所带来的心血管反应及免疫抑制,降低了老年患者麻醉管理的难度和风险。在其他类型的麻醉场景中,右美托咪定联合艾司氯胺酮也可改善患者的术后恢复质量,减轻术后疼痛程度。在 Huang 等[24]关于乳腺癌患者的麻醉研究中,右美托咪定联合艾司氯胺酮不仅可减轻术后炎症反应和神经损伤,还可控制疼痛并减少患者对阿片类药物的需求,进而提高患者的术后康复质量。一项有关腹腔镜胆囊手术的研究也显示,右美托咪定联合艾司氯胺酮可提高手术质量,缓解患者术后躁动,加速患者认知功能的恢复,猜测可能与艾司氯胺酮可通过刺激交感神经系统直接抑制应激反应有关[25]。可见,右美托咪定联合艾司氯胺酮可被应用于麻醉管理,具有一定的安全性、有效性。

2.2.3　咪达唑仑　咪达唑仑是一种强力镇静剂,可口服、鼻滴、肌肉注射、静脉注射,具有起效快、副作用少及排泄快的特点。对于脑损伤患者,使用咪达唑仑联合艾司氯胺酮进行麻醉可调节围术期炎症反应,改善患者颅内压,从而避免术后躁动、低血压等不良反应的发生[26]。区锦辉等[27]研究指出,咪达唑仑联合艾司氯胺酮能够优势互补,镇静效果理想,可有效降低老年下肢骨折患者的交感神经异常兴奋的情况,有助于稳定患者血流动力学,减少肾上腺皮质激素分泌,减轻患者对手术的应激反应。Wang 等[28]的研究发现,采用鼻滴艾司氯

胺酮联合口服咪达唑仑的方式进行无创麻醉，与静脉注射相比成功率更高，镇静效果更好，可缓解患儿对牙科治疗的恐惧及焦虑心理，提升其配合程度。周思易等[29]在另一项关于儿童四肢病损切除术的研究中同样发现，艾司氯胺酮滴鼻联合口服咪达唑仑起效及患者术后恢复速度快，且可发挥药物的协同作用，减少两类药物的单独使用剂量，从而降低了多种不良反应发生的可能性。

2.2.4　罗哌卡因　罗哌卡因是一种长效局部麻醉药，其毒性较小，常用于硬膜外阻滞麻醉，其与其他麻醉药物联合使用可帮助延长麻醉持续时间、减少术后镇痛药的使用。罗哌卡因与艾司氯胺酮的联合使用常见于产妇分娩及部分骨科手术中。据报道，罗哌卡因联合艾司氯胺酮不仅在分娩时可发挥镇痛作用，还可改善大脑功能，显著降低分娩后抑郁的发生率，猜测可能与血清中瘦素、去甲肾上腺素和肾上腺素的调节有关[30]。郭强等[31]研究显示，对下肢踝部骨折手术的患者采用罗哌卡因复合艾司氯胺酮阻滞麻醉，镇痛效果与罗哌卡因复合舒芬太尼的效果相当，且具有较好的镇痛满意度，也并未提升不良反应的发生率。一项关于上肢骨折患者的麻醉管理研究同样显示，罗哌卡因联合艾司氯胺酮用于上臂丛神经阻滞具有较好的麻醉效果，可降低阻滞后反跳痛的发生率，增加手术安全性，同时还能降低患者术后舒芬太尼的用量，有利于患者术后恢复[32]。罗哌卡因联合艾司氯胺酮同样可应用于老年患者的骨折手术麻醉管理中，与单纯采用罗哌卡因相比，罗哌卡因联合艾司氯胺酮并不会缩小神经阻滞范围，也不会影响患者认知功能及神经功能的恢复，具有一定安全性[33]。

2.2.5　舒芬太尼　舒芬太尼是一种强效阿片类镇痛药，具有较好的镇痛效果和较长的镇痛持续时间，但应用剂量过大较易引起呼吸抑制、循环抑制等多种不良反应，且存在一定依赖性，使其在临床应用中受到了一定限制。艾司氯胺酮除具有镇痛、镇静和麻醉作用外，对阿片类药物引起的痛觉过敏也有一定的预防作用，其代谢及苏醒更快、神经系统不良反应轻、呼吸道分泌物少，具有明显的神经保护作用。Yan 等[34]认为，在应用舒芬太尼时加入艾司氯胺酮可提高麻醉的质量和效果，减少舒芬太尼的用量，从而限制药物潜在的不良反应，使其可以更安全地运用于临床工作之中。李洪超等[35]研究显示，舒芬太尼联合艾司氯胺酮应用于髋关节置换术可取得满意的镇痛效果，同时还降低了患者苏醒期躁动的情况，猜测与艾司氯胺酮能通过提高机体对二氧化碳的敏感性逆转舒芬太尼所引起的呼吸抑制作用有关。一项有关宫腔镜手术的研究发现，亚麻醉剂量艾司氯胺酮辅助舒芬太尼进行麻醉够稳定患者的血压和心率，减少术后疼痛和舒芬太尼围术期的消耗，同时改善患者的焦虑情绪，进而提高了患者的治疗满意度[36]。Saugel 等[37]研究也显示，与单一使用舒芬太尼相比，联合静脉注射艾司氯胺酮的患者在全身麻醉过程中循环更为平稳，且术后消耗的阿片类药物更少，疼痛评分明显更低。可见，舒芬太尼联合艾司氯胺酮是效率更高的用药方案，不仅能有效的镇痛，还能减少舒芬太尼引起的不良反应，提高麻醉的安全性。

3　小　结

艾司氯胺酮因其安全性高、可控性好的优势，在多种手术场景、与多种麻醉药物的联合应用中都取得了较好的效果。艾司氯胺酮的副作用相对较小，仅在大剂量使用时会出现心率、血压升高及呼吸抑制的情况。艾司氯胺酮不仅具有较强的镇痛、镇静作用，还能改善患者术后认知功能及负面情绪，具有广阔的临床应用前景。但艾司氯胺酮目前在我国仍属于新药范畴，临床应用经验相对不足，因此未来仍需要许多前瞻性、大样本、涉及不同手术类型的试验研究。

利益冲突　无

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