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Perioperative opioid-free anesthesia: advances in the combined application of esketamine and dexmedetomidine

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Abstract: Opioids will cause adverse effects such as postoperative gastrointestinal reactions, respiratory depression, hyperalgesia, and addictive potential. Recent studies have advocated for reducing or eliminating opioid use to improve postoperative recovery quality of patients. Esketamine and dexmedetomidine have gained widespread clinical application due to their analgesic, anti-inflammatory, and psychomodulatory properties. This article systematically reviews the clinical advancements in the application of esketamine and dexmedetomidine in perioperative opioid-free anesthesia, evaluating their impact on postoperative recovery outcomes. The combination of these two drugs can reduce postoperative pain, nausea and vomiting, and improve patient satisfaction. The combination demonstrates the safety and efficacy as opioid alternatives in perioperative management.

Keywords: Esketamine; Dexmedetomidine; Opioid-free anesthesia; Postoperative recovery; Perioperative management

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Opioids play an important role in perioperative pain management. However, the extensive use of opioids during the perioperative period may cause adverse reactions such as nausea and vomiting, hyperalgesia, respiratory depression, and drug addiction [1-2], which seriously affect the quality of postoperative recovery and reduce patient comfort. In recent years, opioid-free anesthesia (OFA) has been widely used clinically due to its safety and effectiveness. The drugs mainly include esketamine, dexmedetomidine, lidocaine, benzodiazepines, and non-steroidal anti-inflammatory drugs [3]. Among them, esketamine, as the dextrorotatory enantiomer of ketamine, primarily acts as a non-competitive antagonist on the N-methyl-D-aspartic acid (NMDA) receptor, producing sedative and analgesic effects, with a potency approximately twice that of ketamine. Furthermore, compared with ketamine, esketamine has characteristics such as a shorter recovery period, less postoperative pain, faster recovery of cognitive function, and a lower incidence of psychiatric side effects [4]. Dexmedetomidine has a selective α2-adrenergic receptor agonist effect. By activating receptors in the locus coeruleus, it inhibits sympathetic nerve activity and reduces the release of norepinephrine, possessing characteristics such as analgesia, sedation, antisympathetic, anxiolytic, anti-inflammatory, and inhibition of nausea and vomiting, without causing respiratory depression [5-6]. This article comprehensively analyzes the latest progress in various aspects of the clinical application of esketamine and dexmedetomidine, including stress response, postoperative analgesia, cognitive function, and the incidence of postoperative adverse reactions, to provide references for selecting safer and more effective anesthesia protocols in clinical practice, thereby optimizing the patient's surgical experience and postoperative recovery process.

1 Clinical Effects of the Combination of Esketamine and Dexmedetomidine

1.1 Stress Response

During the perioperative period, patients often face significant physiological and psychological stress

processes. The endocrine changes caused by adverse stress may affect the overall quality of postoperative recovery. During anesthesia induction and intubation, patients' hemodynamics are prone to dramatic fluctuations, manifesting as a "roller coaster" phenomenon, i.e., initial hypotension and bradycardia, followed by a significant increase in blood pressure and heart rate [7]. However, for patients with coronary heart disease, aneurysms, or refractory hypertension, intense intraoperative hemodynamic fluctuations may lead to serious adverse events such as myocardial ischemia or aneurysm rupture. Therefore, controlling the intraoperative stress response is particularly important. Dexmedetomidine has sedative and analgesic effects and can slow the heart rate by inhibiting the sympathetic response. Esketamine is an isomer of ketamine, with lower sympathomimetic effects compared to ketamine, and possesses sedative and analgesic effects, maintaining a good level of analgesia at lower doses [5]. A randomized controlled trial showed that adjuvant anesthesia induction with either dexmedetomidine or esketamine can reduce cardiovascular stimulation symptoms caused by double-lumen endotracheal intubation [8]. A meta-analysis by Bell *et al.* [9] found that ketamine can reduce intraoperative blood pressure variability; esketamine, as the dextrorotatory isomer of ketamine, has similar effects. Another study on pediatric bronchoscopy also proved that the sedation and analgesia process with the combination of dexmedetomidine and esketamine resulted in more stable circulation and a lower incidence of adverse reactions [10].

Some research results indicate that these two drugs have a synergistic effect when used in combination during the perioperative period [11]. Relying on the mild respiratory depressant effect of dexmedetomidine and esketamine's enhancement of the respiratory center's sensitivity to carbon dioxide, the combined use of these two drugs in awake intubation for difficult airways can reduce respiratory depression while maintaining hemodynamic stability and alleviating patient discomfort [7]. The adjuvant use of dexmedetomidine and esketamine for intraoperative intubation is safe and effective. Infusion of a loading dose of dexmedetomidine during induction can inhibit the sympathetic response, reduce catecholamine release, and suppress the stress response from laryngoscopy and intubation [12]. Additionally, adjuvant induction with 0.3 mg/kg esketamine can maintain more stable hemodynamics in patients during double-lumen endotracheal intubation. This is related, on one hand, to esketamine increasing cardiac output, and on the other hand, to its analgesic and anti-inflammatory effects reducing the stimulation of the airway mucosa [13-14]. However, there is relatively little research on the combination of dexmedetomidine and esketamine for controlling intraoperative stress response, and further clinical studies are still needed to explore their synergistic effects.

1.2 Analgesic Effect

The analgesic effect of dexmedetomidine is caused by activating α2-adrenergic receptors in the central and peripheral nervous systems [15]. Esketamine primarily acts on NMDA receptors and activates opioid, monoaminergic, glutamatergic, and muscarinic systems to produce analgesic effects [16]. Previous studies found that compared to an opioid-based induction regimen, an opioid-free regimen induced with a combination of dexmedetomidine and esketamine showed no significant difference in pain scores at 24 hours postoperatively in patients undergoing thoracoscopic lobectomy. Furthermore, compared to the opioid group, the application of dexmedetomidine and esketamine improved pain scores at 24–48 hours postoperatively [2], which may be related to their analgesic mechanisms. Relevant research suggests that pain is not equivalent to nociception; pain is a conscious perception of noxious stimuli during the perioperative period. The mechanism of analgesia during general anesthesia involves inhibiting the response to nociceptive stimuli and reducing the impact of harmful stimulatory mediators, such as serotonin, peptides, and norepinephrine [1]. Inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) can activate tryptophan and indoleamine 2,3-dioxygenase in the body and have been proven to be associated with elevated levels of serotonin and catecholamines [17]. Kurexi *et al.* [18], analyzing literature from 2000 to 2022 on opioids and immune function, found that opioid abuse damages the immune system, increases the release of inflammatory mediators, leading to postoperative hyperalgesia and the formation of chronic pain [19-20]. The use of drugs such as dexmedetomidine, esketamine, non-steroidal anti-inflammatory drugs, and lidocaine can reduce perioperative opioid consumption and enhance the analgesic effect. An important mechanism herein is the modulation of the inflammatory immune system and inhibition of the production of noxious stimulatory substances. For example, dexmedetomidine and esketamine can inhibit IL-1, TNF-α, etc., reducing the generation of noxious stimulatory substances [16, 21-22], thereby producing an analgesic effect, subsequently lowering patients' postoperative pain scores, which is also one of the mechanisms for improving postoperative cognitive function and exerting anti-anxiety and antidepressant effects. Studies have found that the combination of dexmedetomidine and esketamine to some extent improved the quality of postoperative recovery in patients undergoing modified radical mastectomy for breast cancer, reduced postoperative pain intensity, and decreased the incidence of bradycardia and rescue analgesia [23]. Therefore, some clinical studies advocate the combined use of dexmedetomidine and esketamine for sedation and analgesia to reduce the application of perioperative opioids and their adverse reactions [1]. However, current research is concentrated in minor surgeries with less painful stimulation, such as mastectomy, cholecystectomy, and spinal correction [24-25], and there is still a lack of universal studies proving the analgesic efficacy of dexmedetomidine and

esketamine for moderate to severe pain.

1.3 Sedative Effect

Both dexmedetomidine and esketamine have sedative and hypnotic effects. Using dexmedetomidine can produce a sedative effect similar to natural sleep, and with increasing dose, the N2 and N3 stages of physiological sleep are prolonged. Esketamine, by inhibiting glutamate entry into the NMDA receptor-mediated γ-aminobutyric acid (GABA)ergic neuronal system, causes excitation of the central nervous system, leading to changes in cortical and limbic system excitability, ultimately resulting in loss of consciousness [10]. Due to their weak respiratory depressant effects, they have high safety when used in some uncooperative populations. In pediatric magnetic resonance imaging examinations, esketamine and dexmedetomidine, respectively combined with propofol, increased the success rate of sedation and resulted in higher satisfaction among examining physicians [5]. Another study indicated that children receiving intranasal sedation with a combination of dexmedetomidine and esketamine cooperated better during anesthesia induction, but using esketamine alone might increase the incidence of postoperative agitation [4]. It is worth noting that dexmedetomidine and esketamine achieved better therapeutic effects in patients with refractory insomnia, with lower incidences of respiratory depression, hypoxemia, and bradycardia [26], suggesting they may play an important role in sleep medicine and are expected to provide safe and comfortable sleep therapy for insomniacs. However, dexmedetomidine, as a medium to long-acting sedative, when combined with esketamine for anesthesia induction and maintenance, can lead to issues such as excessive sedation, prolonged awakening time, and extended stay in the post-anesthesia care unit (PACU) [1, 23]. Therefore, the selection of patients should be cautious, especially for elderly patients prone to delayed recovery.

1.4 Anti-anxiety and Antidepressant Effects

A review concerning laparoscopic, gynecological, obstetric, and cardiovascular surgeries reported the incidence of perioperative anxiety and depression to be as high as 80%–89% [27]. Severe anxiety and depression can prolong hospital stays, increase the economic burden on patients, and affect the efficacy of postoperative recovery. In 2019, the US Food and Drug Administration approved ketamine and esketamine for use as antidepressant drugs [28]. Similar to ketamine, esketamine not only has NMDA receptor antagonistic effects but also modulates GABA, brain-derived neurotrophic factor (BDNF), opioid receptors, and the monoamine system. Esketamine inhibits GABAergic interneurons, leading to glutamate production, which activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, promoting the release of BDNF and vascular endothelial growth factor (VEGF). BDNF and VEGF bind to their respective targets (i.e., TrkB and Flk-1 receptors), activating intracellular pathways to release mammalian target of rapamycin (mTOR), thereby promoting the expression of presynaptic and postsynaptic proteins, such as Synapsin1, postsynaptic density protein 95 (PSD95), and glutamate receptor 1 (GluR1). These proteins facilitate neuronal maturation and synaptic strengthening, establishing better cortico-limbic connections, which is also one of the important mechanisms for antidepressant effects [29-30]. Research suggests that ketamine and its metabolites stimulate the formation of synaptic connections in brain neurons, which might be related to the inhibitory discharge of lateral habenula (LHb) neurons, thereby improving cognitive and depression levels in rats [31].

On the other hand, the anti-anxiety and antidepressant effects of ketamine may be related to the regulation of inflammatory cell levels. A randomized controlled trial found that in patients with refractory depression accompanied by pain, continuous infusion of ketamine six times led to decreased levels of inflammatory factors such as IL-6 and TNF-α after 2 weeks, and depressive symptoms improved [32]. However, a review on ketamine treatment for depression reported no statistically significant differences in inflammatory factors at baseline and longitudinal levels [33]. The reasons for the discrepant results may be related to bias, the fact that inflammatory cytokine levels cannot immediately reflect the state of depression, and loss of follow-up data. In summary, currently, ketamine and esketamine, as antidepressant drugs, have obvious therapeutic effects on acute depression. There is a need to expand regions and establish multi-center, large-sample trials to verify their anti-anxiety and antidepressant effects during the perioperative period.

Dexmedetomidine is also recognized to have anti-anxiety and antidepressant effects. Some animal experiments have found that dexmedetomidine can improve anxiety-like behavior and cognitive function in rats [34]. This has also been validated in clinical trials. A large meta-analysis including 13 studies found that intranasal administration of dexmedetomidine was more effective than intranasal midazolam in improving preoperative separation anxiety in children [35]. Dexmedetomidine can also reduce postoperative depression scores in parturients [36]. This may be related to dexmedetomidine's ability to inhibit norepinephrine release, reduce levels of immune cytokines IL-6 and TNF-α, improve neurocognitive function, regulate sleep, and alleviate chronic pain. Therefore, it is also considered a potential drug for treating stress-related psychology in mental illnesses, such as anxiety, depression, and post-traumatic stress disorder, following esketamine [37].

Both dexmedetomidine and esketamine can improve anxiety and depression. Huang *et al.* [23] explored that after a loading dose, continuous infusion of dexmedetomidine 0.4 μg/(kg·h) and esketamine 2 μg/(kg·min) could better improve postoperative depression and reduce adverse reactions in breast cancer patients. An experiment suggested that both

dexmedetomidine and esketamine can inhibit the STING/TBK pathway to regulate endoplasmic reticulum phagocytosis in rats with spinal nerve ligation, thereby reducing endoplasmic reticulum stress and thus providing anti-anxiety and anti-nociceptive effects [38]. This benefits from their functions of sedation and hypnosis, sleep quality regulation, chronic pain relief, neuroinflammation modulation, and neurocognitive improvement, leading to their widespread use in OFA. However, there are few clinical studies on the combination of dexmedetomidine and esketamine for anti-anxiety and depression, and there is a lack of direct assessment of the correlation between psychology and objective inflammatory markers.

1.5 Cognitive Function Effects

Data released by the International Perioperative Cognitive Function Research Center show that the incidence of cognitive dysfunction at 1 week, 3 months, and 2 years postoperatively is 26%, 10%, and 1%, respectively [39]. Postoperative cognitive dysfunction is associated with neuroinflammation, oxidative stress, and apoptosis of nerve cells, with neuroinflammation playing a key role in its occurrence and development [40]. Under the stimulation of various factors such as surgery and anesthesia, peripheral inflammatory factors IL-1, IL-6, TNF-α, etc., pass through the blood-brain barrier directly or via vagus nerve afferent pathways and other signal transduction pathways, inducing microglial activation, increasing the level of inflammatory factors within the central nervous system, decreasing BDNF, damaging nerve cells, and leading to cognitive dysfunction [41-43].

As mentioned above, esketamine and dexmedetomidine can improve cognitive dysfunction by reconstructing synaptic connections in the central nervous system, reducing pro-inflammatory factors, and increasing BDNF, among other mechanisms. Recent studies have shown that ketamine can enhance synaptic plasticity, improve behavioral activities in experimental subjects, and promote BDNF production, providing neuroprotective effects [29-31]. Numerous animal models have also found that dexmedetomidine can improve cognitive behavior in rats and protect learning and memory abilities [34, 39, 44]. A multi-center clinical trial also proved that dexmedetomidine can reduce postoperative cognitive dysfunction in elderly patients [45]. However, a large international multi-center study conducted by Avidan *et al.* [46] concluded that ketamine did not increase or decrease the incidence of postoperative delirium. In 2017, Deiner *et al.* [47] showed that compared with the saline group, patients in the dexmedetomidine group under general anesthesia did not have their internal neurochemical environment affected, nor did it reduce the incidence of postoperative delirium. The aforementioned research results indicate that dexmedetomidine and esketamine can improve patients' postoperative cognitive dysfunction, but the effect on reducing the incidence of acute delirium is not very obvious. Research on dexmedetomidine and esketamine regarding cognitive function is relatively lacking, and the related mechanisms still require extensive clinical and basic research to elucidate.

1.6 Postoperative Nausea and Vomiting (PONV)

Clinical practice has found that besides the discomfort caused by pain to patients, another noteworthy issue is PONV. Relevant studies indicate that the incidence of PONV in patients undergoing thoracoscopic surgery is 20%–60%, associated with factors such as female gender, non-smoking status, history of motion sickness, history of PONV, and postoperative opioid use [2]. Dexmedetomidine, by reducing sympathetic nervous tension and catecholamine production, can reduce the incidence of PONV in patients [23], but esketamine may increase the incidence of PONV [10]. However, Massoth *et al.* [1] found that combined application of esketamine and dexmedetomidine during anesthesia induction in gynecological surgery, compared with the opioid control group, also reduced the incidence and severity of PONV. Furthermore, the study by Feng *et al.* [2] also found the same result, especially the incidence of PONV within 48 hours postoperatively, which was significantly lower in the combination group compared to the opioid group. A Meta-analysis summarized the same conclusion, that perioperative application of esketamine and dexmedetomidine is beneficial for reducing PONV [48]. This may be related to opioid-sparing effects and the antisympathetic action of dexmedetomidine. With the proposal of multimodal analgesia, postoperative pain management for patients has been strengthened, but the occurrence of postoperative PONV also affects patient recovery. The combined application of esketamine and dexmedetomidine can reduce the incidence of PONV in patients and has great potential in promoting the quality of perioperative recovery.

2 Clinical Application of the Combination of Esketamine and Dexmedetomidine

Esketamine and dexmedetomidine are commonly used as adjuncts to traditional anesthesia, aiming to reduce drug dosages and achieve better anesthetic effects. They also serve as intravenous sedative and analgesic adjuvants for regional anesthesia, compensating for its limitations. Furthermore, they play a significant role in procedures requiring patient cooperation and stillness, reducing the incidence of respiratory depression, alleviating patient anxiety, and improving anesthesia satisfaction. In recent years, with the introduction of the OFA, and due to their stable hemodynamics and minimal respiratory depression, they have been widely used in opioid-free anesthesia processes. This includes anesthesia induction and maintenance for various surgeries such as pancreatic, gallbladder, breast, thoracoscopic, and gynecological procedures. Studies have found that compared to traditional opioids, this combination provides equivalent analgesic efficacy, relatively stable intraoperative hemodynamics, while also reducing the incidence of postoperative adverse reactions and

improving recovery quality [1-2, 49-50]. Some scholars have also chosen dexmedetomidine and esketamine for postoperative analgesia, with results showing analgesic scores comparable to opioid-based regimens, and even more stable effects and prolonged duration [24]. However, there is a lack of research on surgical types potentially causing moderate to severe pain. Additionally, dexmedetomidine, being a medium to long-acting sedative, can delay patient awakening and prolong PACU stay. Excessively high doses of esketamine can lead to dizziness, sympathomimetic effects, and psychiatric side effects. Therefore, as potential opioid alternatives, while evaluating their advantages, it is also necessary to explore more suitable drug ratios to improve patient recovery quality, which requires further clinical research for validation.

3 Conclusion

This article has reviewed the clinical application of esketamine and dexmedetomidine in perioperative OFA, revealing the significant potential of this drug combination in improving the quality of patient postoperative recovery. Compared to conventional opioid-based anesthesia regimens, the combined use of esketamine and dexmedetomidine demonstrates significant advantages in reducing postoperative pain scores, decreasing the incidence of PONV, improving patient satisfaction, and promoting early recovery of cognitive function. However, it may lead to adverse effects such as prolonged postoperative recovery time and dizziness. Currently, there is a lack of research findings in specific patient populations and regarding its efficacy in controlling moderate to severe pain.

Furthermore, we note that although the combined use of esketamine and dexmedetomidine can control the perioperative stress response, inhibit inflammatory reactions, and exert anti-anxiety and antidepressant effects, thereby providing new strategies for perioperative management, there is relatively little research on the synergistic effects of these two drugs. Future efforts should focus on exploring the optimal combination dosage of these two agents to maximize therapeutic efficacy while minimizing potential side effects.

In summary, the combined application of esketamine and dexmedetomidine provides an effective OFA strategy for perioperative management and is expected to improve the quality of postoperative patient recovery. Future clinical studies should further verify these findings and explore their applicability across different surgical types and patient populations to promote the widespread adoption of this treatment approach.

Conflict of Interest None

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·学术前沿·

围手术期无阿片化麻醉:艾司氯胺酮与右美托咪定的联合应用进展

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摘要：阿片类药物会引起术后胃肠道反应、呼吸抑制、痛觉过敏以及药物成瘾等不良副作用,近年研究提出减少或不使用阿片类药物的理念,目的在于提高患者术后恢复质量。艾司氯胺酮和右美托咪定因具有镇痛、抗炎、改善心理等作用在临床中被广泛应用。本文系统性回顾艾司氯胺酮与右美托咪定在围手术期无阿片化麻醉中的临床应用进展,评估其临床应用对患者术后恢复的影响。二者联合应用可减少术后疼痛、恶心呕吐及改善患者满意度。艾司氯胺酮和右美托咪定联合应用可作为阿片类药物的替代方案在围手术期管理中具有安全性和有效性。

关键词：艾司氯胺酮；右美托咪定；无阿片化麻醉；术后恢复；围手术期管理

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Perioperative opioid-free anesthesia: advances in the combined application of esketamine and dexmedetomidine

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Abstract: Opioids will cause adverse effects such as postoperative gastrointestinal reactions, respiratory depression, hyperalgesia, and addictive potential. Recent studies have advocated for reducing or eliminating opioid use to improve postoperative recovery quality of patients. Esketamine and dexmedetomidine have gained widespread clinical application due to their analgesic, anti-inflammatory, and psychomodulatory properties. This article systematically reviews the clinical advancements in the application of esketamine and dexmedetomidine in perioperative opioid-free anesthesia, evaluating their impact on postoperative recovery outcomes. The combination of these two drugs can reduce postoperative pain, nausea and vomiting, and improve patient satisfaction. The combination demonstrates the safety and

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efficacy as opioid alternatives in perioperative management.

Keywords: Esketamine; Dexmedetomidine; Opioid-free anesthesia; Postoperative recovery; Perioperative management

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阿片类药物在围手术期疼痛管理中扮演着重要角色,但围手术期中大量使用阿片类药物可能引起恶心呕吐、痛觉过敏、呼吸抑制及药物成瘾等不良反应[1-2],严重影响患者术后恢复质量和降低患者术后舒适度。近些年来,无阿片化麻醉(opioid-free anesthesia,OFA)因其安全性和有效性在临床上广泛应用,药物主要包括艾司氯胺酮、右美托咪定、利多卡因、苯二氮䓬类、非甾体类药物[3]。其中艾司氯胺酮作为氯胺酮的右旋对映体,主要对N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid,NMDA)受体起非竞争性拮抗作用,产生镇静镇痛效果,其效力大约是氯胺酮的两倍。另外与氯胺酮相比,艾司氯胺酮具有恢复期短、术后疼痛轻、认知功能恢复快、精神副反应发生率低等特点[4]。右美托咪定具有选择性α2肾上腺素能受体激动作用,通过激动蓝斑核受体,抑制交感神经活动,减少去甲肾上腺素的释放,具有镇痛、镇静、抗交感神经、抗焦虑、抗炎症、抑制恶心呕吐等特点,且无呼吸抑制作用[5-6]。本文综合分析艾司氯胺酮与右美托咪定在临床应用中关于应激反应、术后镇痛、认知功能和术后不良反应发生率等多方面的最新进展,为临床选择更为安全有效的麻醉方案提供参考,从而优化患者的手术体验和术后恢复过程。

1 艾司氯胺酮与右美托咪定联用的临床效果

1.1 *应激反应* 在围手术期过程中,患者经常面临着显著的生理和心理应激过程,不良应激引起的内分泌变化可能影响患者术后整体恢复质量。在麻醉诱导和插管期间患者血流动力学容易发生剧烈波动,表现为“过山车”现象,即先是低血压和心动过缓,随后是血压和心率的显著增高[7]。但对于合并冠心病、动脉瘤、顽固性高血压的患者,术中强烈的血流动力学波动可能导致心肌缺血、动脉瘤破裂等严重不良事件发生,因此控制术中的应激反应尤为重要。右美托咪定具有镇静镇痛作用,可以通过抑制交感神经反应减慢心率。艾司氯胺酮是氯胺酮的异构体,较氯胺酮拟交感神经作用更低,具有镇静镇痛作用,可在较低剂量保持较好的镇痛水平[5]。一项随机对照试验表明以右美托咪定或艾司氯胺酮辅助麻醉诱导,可以降低双腔气管插管引起的心血管刺激症状[8]。Bell等[9]的一篇荟萃分析发现,氯胺酮能够降低术中血压变异性,艾司氯胺酮作为氯胺酮的右旋异构体,二者作用相似。另一项小儿气管镜的检查也同样证明了右美托咪定联合艾司氯胺酮镇静镇痛过程循环更稳定,不良反应的发生率更低[10]。

有研究结果表明这两种药物在围手术期联合使用时具有协同效应[11]。依赖于右美托咪定的轻微呼吸抑制作用和艾司氯胺酮对呼吸中枢二氧化碳敏感性的增强,在困难气道清醒插管中,联合使用这两种药物可以减少呼吸抑制,同时维持血流动力学的稳定,减轻患者的痛苦[7]。右美托咪定和艾司氯胺酮辅助用于术中插管具有安全性和有效性。诱导期间输注负荷剂量的右美托咪定可抑制交感神经反应,减少儿茶酚胺的释放,抑制喉镜检查和插管的应激反应[12]。另外,0.3 mg/kg艾司氯胺酮辅助诱导能使患者在双腔气管插管过程中保持更平稳的血流动力学。这一方面和艾司氯胺酮增加心输出量有关,另一方面艾司氯胺酮的镇痛抗炎作用可以减轻对气道黏膜的刺激[13-14]。然而,关于右美托咪定和艾司氯胺酮联合用药控制术中应激反应的相关研究较少,仍需要进一步临床研究去探索二者的协同作用。

1.2 *镇痛效应* 右美托咪定镇痛作用是通过激活中枢和外周神经系统的α2肾上腺素能受体引起的[15]。艾司氯胺酮主要作用于NMDA受体,激活阿片类、单胺能、谷氨酸能和毒蕈碱系统,起到镇痛效果[16]。既往研究发现以右美托咪定联合艾司氯胺酮诱导的无阿片化方案同阿片类药物诱导方案对比,接受胸腔镜下肺叶切除术的患者术后24 h疼痛评分无明显差异,同时相较阿片化组,右美托咪定和艾司氯胺酮的应用对术后24~48 h的疼痛评分有改善作用[2],这可能与两者的镇痛机制有关。相关研究认为疼痛不等于伤害感受,疼痛是围手术期对伤害刺激的一种有意识的感知,全麻过程中镇痛的机制是抑制伤害感受刺激反应,减少有害刺激介质的影响,如血清素、多肽、去甲肾上腺素等[1]。而肿瘤坏死因子-α(TNF-α)、白细胞介素1(IL-1)、白细胞介素6(IL-6)等炎症因子可以激活体内的色氨酸和吲哚胺2,3-双加氧酶,被证明与体内的血清素、儿茶酚胺等水平升高相关[17]。Kurexi

等[18]分析2000年至2022年阿片类药物与免疫功能相关文献发现，滥用阿片类药物会损伤免疫系统，增加炎症介质释放，导致术后痛觉过敏与慢性疼痛形成[19-20]。右美托咪定、艾司氯胺酮、非甾体类药物、利多卡因等药物的使用，可以减少围手术期阿片类药物消耗，增强镇痛效应。这其中一个重要机制就是调节炎症免疫系统，抑制伤害刺激物质产生，如右美托咪定和艾司氯胺酮可抑制IL-1、TNF-α等，降低伤害刺激物质的生成[16,21-22]，起到镇痛效应，进而降低患者术后疼痛评分，这也是改善术后认知功能、抗焦虑抑郁的机制之一。研究发现，右美托咪定联合艾司氯胺酮在一定程度上提高了乳腺癌改良根治术患者的术后恢复质量，减轻了术后疼痛强度，降低了心动过缓和抢救性镇痛的发生率[23]。因此在一些临床研究中提倡右美托咪定、艾司氯胺酮复合镇静镇痛，减少围手术期阿片药物的应用及其不良反应[1]。但目前研究集中在短小、疼痛刺激较小的乳腺切除、胆囊切除、脊柱矫正等手术中[24-25]，仍缺乏普遍性研究证明右美托咪定和艾司氯胺酮对中重度疼痛的镇痛效应。

1.3 镇静效应 右美托咪定和艾司氯胺酮都有镇静催眠的作用，使用右美托咪定可以产生类似于自然睡眠的镇静效应，并且随着剂量增加，生理睡眠N2和N3时期延长。艾司氯胺酮则通过抑制谷氨酸进入NMDA受体介导的γ-氨基丁酸（γ-aminobutyric acid，GABA）能神经元系统，引起中枢神经系统兴奋，导致皮质和边缘系统兴奋性改变，最终导致意识丧失[10]。由于两者对呼吸抑制作用微弱，在一些无法配合的人群中应用具有较高的安全性。在儿童的核磁共振检查中，艾司氯胺酮和右美托咪定分别联合丙泊酚增加镇静成功率，使得检查医师的满意程度较高[5]。另有研究表明，右美托咪定联合艾司氯胺酮滴鼻镇静的患儿更能配合麻醉诱导，但单独使用艾司氯胺酮可能增加术后躁动的发生率[4]。值得注意的是右美托咪定和艾司氯胺酮在治疗顽固性失眠的患者上取得更好的治疗效果，使患者呼吸抑制、低氧血症、心动过缓等发生率更低[26]，提示在睡眠医学治疗过程中可能具有重要的作用，有望为失眠患者提供安全舒适的睡眠治疗。然而，右美托咪定作为中长效镇静药物，与艾司氯胺酮的联合麻醉诱导维持，术后可出现镇静过度、苏醒时间延长、麻醉恢复室（post-anesthesia care unit，PACU）停留时间延长等问题[1,23]。因此，应用时应该慎重选择对象，特别对容易出现苏醒延迟的老年患者。

1.4 抗焦虑抑郁效应 一篇关于腹腔镜、妇产科和心血管手术的综述报告了围手术期焦虑抑郁的发生率高达80%~89%[27]。严重的焦虑抑郁会延长患者的住院时间，增加患者的经济负担，影响患者术后的恢复治疗效果。2019年美国食品药物监督管理局批准氯胺酮与艾司氯胺酮作为抗抑郁药物使用[28]。与氯胺酮相似，艾司氯胺酮不仅有NMDA受体拮抗作用，还能调节GABA、脑源性神经营养因子（brain derived neurotrophic factor，BDNF）、阿片类药物受体和单胺系统。艾司氯胺酮通过抑制GABA能中间神经元，产生谷氨酸，激活α-氨基-3-羟基-5-甲基-4-异噁唑丙酸（AMPA）受体，促进BDNF和血管内皮生长因子（vascular endothelial growth factor，VEGF）释放，BDFN和VEGF与其各自的靶目标（即TrkB和Flk-1受体）结合激活细胞内途径释放雷帕霉素（mTOR），从而促进突触前和突触后蛋白的表达，如突触素1（synapsin1）、突触后密度蛋白95（PSD95）和谷氨酸受体1（GluR1），这些蛋白有利于神经元成熟和突触强化，建立更好的皮质-边缘连接，潜在地改善整体认知功能，也是抗抑郁的重要机制之一[29-30]。研究提示氯胺酮及其代谢产物刺激大脑神经元突触连接的形成，可能与外侧缰核（LHb）神经元的抑制放电有关，从而起到改善大鼠的认知与抑郁水平[31]。

另一方面，氯胺酮的抗焦虑抑郁作用可能与调节炎症细胞水平相关。一项随机对照研究发现，在难治性抑郁伴有疼痛的患者中，连续输注6次氯胺酮，2周后炎症因子IL-6、TNF-α等水平下降，抑郁样症状得到改善[32]。然而一项氯胺酮治疗抑郁的综述中报告了炎症因子在基线水平和纵向水平并无统计学差异[33]，造成结果差异性的原因可能与偏倚、炎症细胞因子水平不能即刻反映抑郁症状态和随访数据的丢失有关。总而言之，目前氯胺酮及艾司氯胺酮作为抗抑郁的药物，对急性抑郁的治疗效果明显，需要扩大区域、建立多中心的大样本试验来验证围手术期的抗焦虑抑郁作用。

右美托咪定也被认定具有抗焦虑抑郁的作用。在一些动物实验中发现右美托咪定能够改善大鼠的焦虑样行为及认知功能[34]。在临床试验中也同样得到验证。一项包含13项研究的大型荟萃分析发现，与鼻内给予咪达唑仑相比，鼻内滴入右美托咪定在改善儿童的术前分离焦虑更有效[35]，右美托咪定还可以降低产妇的术后抑郁评分[36]。这可能与右美托咪定能抑制去甲肾上腺素的释放、降低免疫细胞因子IL-6和TNF-α水平、改善神经认知功能、调节睡眠、缓解慢性疼痛相关。因此其也被认为是继艾司氯胺

酮后治疗精神疾病中压力心理如焦虑、抑郁、创伤性应激障碍的潜力性药物[37]。

右美托咪定与艾司氯胺酮都可以改善焦虑抑郁情况。Huang 等[23]探究给予负荷剂量后持续输注右美托咪定 0.4 μg/(kg·h)和艾司氯胺酮 2 μg/(kg·min)能更好地改善乳腺癌患者术后抑郁和减少不良反应。一项基础实验认为右美托咪定及艾司氯胺酮都可以抑制 STING/TBK 途径调节脊神经结扎大鼠内质网吞噬功能，来减轻内质网应激，从而提供抗焦虑和抗伤害作用[38]。这得益于两者具有镇静催眠、调节睡眠质量、缓解慢性疼痛、调节神经炎症，改善神经认知的功能，在 OFA 广泛应用。然而右美托咪定与艾司氯胺酮联合抗焦虑抑郁的临床研究较少，缺乏对心理以及与炎症客观指标相关性的直接评估。

1.5　*认知功能效应*　国际围手术期认知功能研究中心发布的数据显示，术后 1 周、3 个月和 2 年认知功能障碍的发生率分别为 26%、10%、1%[39]。术后认知功能障碍与神经炎症、氧化应激、神经细胞的凋亡有关，其中神经炎症在术后认知功能障碍的发生和发展中起着关键作用[40]。在手术及麻醉等多种因素刺激作用下，外周炎症因子 IL-1、IL-6、TNF-α等通过直接透过血脑屏障或迷走神经传入通路和其他信号传导通路，诱导小胶质细胞激活，增加中枢内的炎症因子水平，降低 BDNF，损伤神经细胞，导致认知功能障碍[41-43]。

正如上述所言，艾司氯胺酮和右美托咪定可以通过重构中枢神经的突触连接、降低促炎因子、增加 BDNF 等改善认知功能障碍。近些年来的研究表明氯胺酮可以增强神经突触的可塑性，改善实验对象的行为活动，同时促进 BDNF 产生，提供神经保护作用[29-31]。大量动物模型也发现右美托咪定可以改善大鼠的认知行为，保护学习和记忆能力[34,39,44]。一项多中心临床试验同样证明右美托咪定可以降低老年患者术后认知功能障碍[45]。然而 Avidan 等[46]进行的一项大型国际多中心研究得出，氯胺酮并不会增加或降低术后谵妄的发生率。2017 年 Deiner 等[47]研究表明，与生理盐水组相比，右美托咪定组患者在全身麻醉状态下并不影响机体内神经化学环境，也不能降低术后谵妄发生率。上述研究结果表明右美托咪定和艾司氯胺酮可以改善患者术后认知功能障碍，但对降低急性谵妄的发生率效果不太明显。关于右美托咪定和艾司氯胺酮对认知功能的研究相对缺乏，相关机制仍需要进行大量的临床研究和基础研究去阐明。

1.6　*术后恶心呕吐*(postoperative nausea and vomiting, PONV)　临床实践发现除了疼痛对患者造成的不适感，另外一个值得关注的问题即 PONV。相关研究表明进行胸腔镜手术的患者 PONV 发生率在 20%~60%，与女性、非吸烟人群、有晕动史、PONV 病史和术后阿片类药物使用等因素相关[2]。右美托咪定通过降低交感神经紧张性，减少儿茶酚胺生成，可降低患者 PONV 的发生率[23]，但艾司氯胺酮可能增加 PONV 的发生率[10]。但 Massoth 等[1]发现在妇科手术麻醉诱导中联合应用艾司氯胺酮和右美托咪定，与阿片类药物对照组相比，也能降低 PONV 的发生率和严重程度。此外 Feng 等[2]的研究也发现相同的结果，尤其是术后 48 h 内 PONV 发生率，联合应用组较阿片化组明显降低。一项 meta 分析中总结出同样的结论，围手术期应用艾司氯胺酮和右美托咪定对于降低 PONV 有益[48]。这可能与节约阿片类药物使用和右美托咪定抗交感作用相关。随着多模式镇痛化的提出，患者的术后痛疼管理得到加强，但术后 PONV 的发生同样使患者的恢复受到影响，艾司氯胺酮与右美托咪定的联合应用可降低患者的 PONV 发生率，在促进围手术期康复质量中具有巨大的潜力。

2　艾司氯胺酮与右美托咪定联用的临床应用

艾司氯胺酮与右美托咪定通常应用于传统麻醉辅助用药，以期减少药物的用量，达到较好的麻醉效果，或作为局部麻醉的静脉麻醉辅助镇静镇痛，弥补局部麻醉的不足，此外在一些需要安静配合的操作中也承担了相当重要的角色，降低呼吸抑制发生，缓解患者的焦虑，提高麻醉的满意度。近些年随着 OFA 理念提出，因其稳定的血流动力学和轻微的呼吸抑制作用，被广泛应用于无阿片化的麻醉过程，如胰腺、胆囊、乳腺、胸腔镜、妇科等多种手术类型的麻醉诱导和麻醉维持，发现与传统阿片类药物相比具有相同的镇痛效果，术中血流动力学相对平稳，同时减少术后不良反应发生率，提高恢复质量[1-2,49-50]。部分学者还选择右美托咪定和艾司氯胺酮作为术后镇痛，结果显示镇痛效果评分与阿片类镇痛方案一致，甚至作用效果更稳定、作用时间延长[24]。但缺乏对可能导致中重度疼痛的手术类型的研究，此外右美托咪定作为中长效的镇静药物，会延迟患者苏醒时间、延长 PACU 停留时间，过大剂量的艾司氯胺酮可导致头晕、拟交感神经、精神系统副作用。因此作为潜力性的阿片替代药物，在评估优势的同时，也需要探究更合适的药物配比，提高患者的康复质量，这在

临床上需要更多的研究去验证。

3 结 语

本文综述了艾司氯胺酮与右美托咪定在围手术期OFA中的临床应用，揭示了这两种药物联合使用在改善患者术后恢复质量方面的显著潜力。对比常规阿片类麻醉方案，艾司氯胺酮和右美托咪定的联合应用在降低术后疼痛评分、减少PONV发生率、改善患者满意度以及促进早期认知功能恢复方面表现出显著优势，但可能导致术后复苏时间延长、头晕等不良反应。目前尚缺乏特殊人群的研究结果以及对中重度疼痛控制效果的研究。

此外，笔者还注意到，虽然艾司氯胺酮和右美托咪定的联合使用可以控制围手术期应激反应、抑制炎症反应、以及抗焦虑抑郁，为围手术期管理提供了新的策略。但关于这两种药物协同作用研究较少，未来应着重探讨二者的最佳配伍剂量，以获取最大化治疗效果并最小化潜在的副作用。

综上所述，艾司氯胺酮与右美托咪定的联合应用为围手术期管理提供了一种有效的OFA方案，有望改善患者的术后恢复质量。未来的临床研究应进一步验证这些发现，并探索在不同手术类型和患者群体中的适用性，以推动这一治疗方案的广泛应用。

利益冲突 无

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