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艾司氯胺酮在改善外科患者围术期焦虑和抑郁中作用的研究进展

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摘 要

围术期焦虑和抑郁是临床常见且严重的心理问题，尤其是术前已被确诊为焦虑和抑郁的患者。艾司氯胺酮是一种N-甲基-D-天冬氨酸(N-methyl-D-aspartic, NMDA)受体拮抗剂，已被证明可通过直接靶向谷氨酸能神经系统快速改善抑郁症状和自杀意念。本文就近年来有关艾司氯胺酮在改善外科患者围术期焦虑和抑郁中的作用进行综述与总结，为改善患者的临床预后提供参考。

关键词

艾司氯胺酮，围术期，抑郁

Research Progress of Esketamine in Improving Perioperative Depression and Sleep Quality

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Abstract

Esketamine is an N-methyl-D-aspartic acid (NMDA) receptor antagonist, which can play the role of anesthesia, analgesia and anti-negative emotions. It is a new clinical anesthetic. During the peri-

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operative period, patients often suffer from depression and poor sleep quality due to nervousness and fear of pain, which is not conducive to the operation and postoperative recovery. Esketamine has a positive effect on anti-depression and improving sleep quality during perioperative period. This paper analyzes and summarizes the clinical application of estaketamine in relieving depression and improving sleep quality in recent years, so as to provide basis for rational use of drugs in clinic.

Keywords

Esketamine, Perioperative Period, Depression

1. 引言

经历麻醉和手术过程对患者是一种不同程度的心理应激；在这种情况下，焦虑和抑郁是常见而严重的心理问题。根据手术人群和测量工具的不同，临床上发生显著的焦虑和抑郁的患病率估计值分别为：焦虑的 5%至 45%，抑郁的 6%至 52% [1] [2]。围术期焦虑和抑郁可能会增加手术并发症的发生风险，并降低患者在康复过程中的参与度，最终影响患者术后的治疗和康复[3]。艾司氯胺酮是一种由氯胺酮分离得到的手性环己酮衍生物，是氯胺酮 S-对映体，其镇静、镇痛效果可以达到左旋氯胺酮的四倍左右，且用药后的不良反应较少，具有麻醉、镇痛、抗负性情绪的作用[4]。近年来，艾司氯胺酮的抗焦虑和抑郁作用已经得到了国际权威认证[5]，其可通过 NMDA 受体发挥强大而持久的抗焦虑和抑郁作用。为此，本文将对艾司氯胺酮的药理作用、抗焦虑抑郁机制、临床应用、治疗现状、药代动力学特点及其应用前景进行综述。

2. 艾司氯胺酮的药理作用

艾司氯胺酮的药理学特征是非选择性、非竞争性拮抗 NMDA 受体，可阻断 γ-氨基丁酸(γ-aminobutyricacid, GABA)中间神经元上的 NMDA 受体，激活 α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionicacidreceptor, AMPAR)，从而增加神经兴奋信号，恢复突触功能[6]，这可能与艾司氯胺酮的抗抑郁作用有关。氯胺酮由右旋氯胺酮(esketamine)和左旋氯胺酮(arketamine)按照 1:1 的比例混合而成，主要在肝脏去甲基化转化为去甲氯胺酮，此代谢过程主要靠细胞色素 P450(CYP)3A4 和 2B6 酶催化，之后再进行一系列代谢转化，部分在肾脏和胆汁中被葡萄糖醛酸化和消除，只有 10%~15%直接被肾脏消除[7]；而艾司氯胺酮则具有更强的去甲基化能力，清除率超出左旋氯胺酮单体 22% [8]。有研究发现，左旋氯胺酮单体仅能抑制神经元的摄取，而艾司氯胺酮还可以抑制神经元外的摄取，进而使去甲肾上腺素水平更大幅度地增加，因此艾司氯胺酮的用药剂量仅为左旋氯胺酮的一半左右，在术中应用对心脏的刺激作用较小，副作用也较轻，从而提高了麻醉的安全性[9]。

3. 艾司氯胺酮抗焦虑和抑郁作用机制

大脑产生负面情绪的原因是外侧缰核的簇状放电，而这种簇状放电的兴奋性递质是谷氨酸门控离子通道 NMDA [10]。艾司氯胺酮作为 NMDA 受体拮抗剂，可快速起效持续阻断 NMDA 受体，阻断真核细胞的延伸因子 2 (Eukaryotic Elongation Factor 2, eEF2)激酶，增加脑源性神经营养性因子(brain-derived

neurotrophic factor, BDNF)的释放及原肌球蛋白受体激酶 B (tropomyosin receptor kinase B, TrkB)的表达，诱导雷帕霉素靶蛋白复合体 1 (mammalian target of rapamycin complex 1, mTORC1)信号通路及细胞外调节蛋白激酶(extra cellular regulated protein kinases, ERK)激活，改善神经可塑性和突触的形成[11]，短时间显著改善患者情绪低落、自我厌恶等负面情绪。简而言之，传统的抗抑郁药物治疗是刺激大脑产生兴奋作用，而艾司氯胺酮则是去除大脑的抑制作用。另有研究显示，艾司氯胺酮还可能通过激活阿片受体来发挥抗抑郁作用[12]，纳曲酮(阿片受体拮抗剂)预处理能够减弱艾司氯胺酮的抗抑郁作用。

4. 艾司氯胺酮的临床应用

4.1. 麻醉镇静与镇痛

艾司氯胺酮的镇痛作用主要体现在两部分，一部分为其可明显减少全麻术中非甾体抗炎药、芬太尼以及术后阿片类药物的使用剂量[13]，另一部分是艾司氯胺酮可缓解由阿片类药物诱发的呼吸抑制、痛觉过敏等不良症状[14] [15]。在目前的临床应用中，艾司氯胺酮不仅可以在全麻手术中发挥作用，还可在关节腔、硬膜外等部位作为局麻药发挥一定的局部阻滞的作用[16]。一方面，硬膜外腔的艾司氯胺酮通过硬脊膜进入脑脊液，阻断了痛觉信号向中枢的传递[17]，达到镇痛和抑制中枢痛觉敏化的效果，还可与中枢阿片 μ 受体结合[18]，发挥镇痛效果；另一方面，艾司氯胺酮为脂溶性药物[19]，可被硬膜外腔吸收入血，发挥镇静镇痛作用。艾司氯胺酮与罗哌卡因等局麻药可能具有协同镇痛效应，联合进行局部阻滞时可增强镇痛效果和延长镇痛时间[20]-[22]。艾司氯胺酮的镇静作用也较强，可通过非竞争性抑制 NMDA 受体产生镇静和遗忘作用，使机体产生一种意识与身体短暂分离的感觉，作为镇静辅助剂有效降低全麻术中吸入性麻药或者静脉注射麻药的用量，一定程度上保证了患者机体循环系统的稳定性[23]-[25]。这些发现支持在围手术期使用艾司氯胺酮作为镇静的辅助剂。

4.2. 抗焦虑和抑郁作用

很多研究表明艾司氯胺酮能更有效地改善围手术期早期焦虑抑郁症状，缓解围术期患者的疼痛，减少围手术期的应激反应，缩短卧床休息时间，促进术后康复，具有良好的临床应用价值[26]-[28]。此外，艾司氯胺酮鼻腔喷雾剂逐渐用于抑郁症的治疗。Andreas R 等[29]的结果显示在这项涉及难治性抑郁症患者的试验中，艾氯胺酮鼻腔喷雾剂在与选择性 5-羟色胺再摄取抑制剂(SSRI)或 5-羟色胺-去甲肾上腺素再摄取抑制剂(SNRI)联合使用时优于比较物缓释喹硫平(一种常用的抗精神病增强剂)。其抗抑郁机制可能是艾氯胺酮对单胺能神经系统的作用靶点，可影响脑干蓝斑，进而影响去甲肾上腺素能系统，促进该基因的转录和表达，增加转运体的合成，导致 NE 从质膜向细胞质迁移，降低血清 NE 和 E 的浓度[30]。

4.3. 改善术后睡眠质量

术后患者常伴有睡眠障碍，除了抗抑郁作用外，艾司氯胺酮被证明可以改善患有重度抑郁障碍和睡眠问题的患者的睡眠障碍，提示艾司氯胺酮有用于治疗睡眠障碍的潜力[31]。已有研究表明，艾司氯胺酮的抗抑郁作用与觉醒、睡眠和昼夜节律的神经生物学结构有关[32]。鉴于艾氯胺酮的镇痛特性，艾司氯胺酮对患者术后睡眠质量和 PSD 的影响可能与阿片类药物消耗的减少有关[33]。Zhang Y 等[34]在研究中将 200 名接受脊柱侧弯矫正手术的患者随机分配到对照舒芬太尼镇痛组(4 μg/kg 在生理盐水中)或联合补充剂组(艾氯胺酮 0.25 mg/ml 和右美托咪定 1 μg/ml)或安慰组，此研究表明小剂量艾氯胺酮–右美托咪定联合用药可安全改善手术后的镇痛和睡眠质量。另有研究表明[35]手术结束前给予亚麻醉剂量艾司氯胺酮能改善乳腺癌患者术后早期的睡眠质量缓解焦虑抑郁情绪，减轻术后疼痛，提高苏醒质量。

目前的研究尚不明确艾氯胺酮对术后睡眠质量和 PSD 预防作用的潜在机制。手术后，患者通常会经

历促炎细胞因子增加、内皮功能障碍、糖囊损伤和中性粒细胞激活，导致 PSD [36]。因此，艾氯胺酮的抗炎作用与可能与 PSD 预防有关。已有一定的实验证明[37]艾司氯胺酮具有调节生物钟基因的作用，进而影响昼夜节律。因此，艾氯胺酮对 PSD 的预防作用可能与昼夜节律系统的调节有关。然而，仍需要进一步的研究来证实昼夜节律在艾司氯胺酮对 PSD 的预防中的作用。

5. 艾司氯胺酮的药代动力学特点

在临床麻醉用药中，艾司氯胺酮具有口服、肌肉注射、静脉注射、滴鼻以及直肠用药等多种给药方式。艾司氯胺酮的生物利用度与给药途径有关，其生物利用度梯度为静脉注射 > 肌肉注射 > 皮下注射 > 鼻内 > 口服[38]。静脉给药是临床常用的方式，生物利用度高达 100%，艾司氯胺酮单次给药 0.125~0.25 mg/kg 即可发挥镇静、镇痛作用，手术时间较长的情况下可采用持续静脉输注的方式来维持患者适当的镇静和镇痛状态[39]。在小儿麻醉诱导中，由于静脉通路的建立比较困难或者不易配合，临床上也经常采用肌内注射的方式给药。另外，由于艾司氯胺酮可在呼吸道局部发挥扩张气管的作用，因此还可以用雾化吸入的方式给药，尤其适用于支气管哮喘的患者[40]。鼻内给药简单方便，也是目前常用的给药方式，但由于此途径药物生物利用度可达 45%，因此需要格外注意其给药剂量。直肠给药的生物利用度较低，为 30%，但对于无法肌内或静脉给药的患者，也可采用直肠给药[41]。

6. 总结与展望

氯胺酮在临床上已使用多年，由于它的许多副作用，已逐渐被其他药物所取代。近年来，人们发现艾司氯胺酮的抗抑郁作用，使它重新出现在公众视野中。目前对其抗抑郁作用进行大量的临床研究，有望为抑郁症患者带来一种新的有效治疗方法。艾司氯胺酮具有比氯胺酮更强的镇痛作用，具有麻醉、镇静、抗抑郁等药理作用，且具有改善围手术期心理状态、改善围术期睡眠质量、预防术后睡眠障碍的作用，对呼吸的影响远小于阿片类镇痛药，使得其在临床麻醉中处于优势地位。然而，目前艾司氯胺酮在围手术期缓解抑郁情绪与改善睡眠质量方面的机制仍然不够明确，仍需要进一步深入研究，以期能够更合理地指导临床应用，使其价值最大化，更好地为患者服务。因此，我们建议将焦虑和抑郁治疗作为围术期管理的一部分，包括教育、心理支持、少阿片类药物镇痛管理、睡眠管理、中枢神经系统兴奋剂以及现有抗抑郁药的延续和优化等，但这需要更多的研究来验证和改进这些策略。

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