

艾司氯胺酮对临床手术患者术后恢复质量的影响的研究进展

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摘要

艾司氯胺酮是氯胺酮的一种异构体, 具有良好的镇静和镇痛作用, 比氯胺酮具有更高的效力和更低的不利反应风险, 广泛应用于围术期麻醉诱导与维持、术后疼痛管理等各方面, 但目前其临床应用的安全性仍存在争议。本文将从患者身体舒适度、情绪状态、神经认知功能以及疼痛感受四个方面, 综述近年来艾司氯胺酮对患者术后恢复质量影响的相关研究进展, 为临床工作提供参考。

关键词

艾司氯胺酮, 麻醉, 术后恢复质量

Research Progress on the Effect of Esmolamine on Postoperative Recovery Quality of Patients Undergoing Clinical Surgery

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Abstract

Esketamine is an isomer of ketamine, which has good sedative and analgesic effects, higher effica-

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cy and lower risk of adverse reactions than ketamine. Esketamine is widely used in perioperative anesthesia induction and maintenance, postoperative pain management and other aspects, but the safety of its clinical application is still controversial. This article will review the recent research progress on the effect of esketamine on postoperative recovery quality from four aspects: physical comfort, emotional state, neurocognitive function and pain perception, so as to provide reference for clinical work.

Keywords

Esketamine, Anesthesia, Postoperative Recovery Quality

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1. 引言

艾司氯胺酮是氯胺酮的右旋体, 与氯胺酮的左旋体相比, 对 N-甲基-D-天冬氨酸(N-methyl-D-aspartate receptor, NMDA)受体有更大的亲和力, 其给药相关的剂量依赖性分离症状的风险较氯胺酮低[1]。艾司氯胺酮同时具备麻醉及镇痛效果, 可用于术前镇静镇痛。除了其麻醉镇痛作用外, 艾司氯胺酮还具有强大的抗抑郁作用[2], 这使得艾司氯胺酮在控制疼痛和情绪改善方面展现出独特的优势, 有利于提高患者术后恢复质量[3]-[8]。麻醉恢复是一个复杂的过程, 往往受多方面因素影响。恢复不良会导致术后并发症增加, 因此提高术后恢复质量对患者具有重要意义。临床上通常采用 Mylse 等人在 2000 年提出的 40 项恢复质量评分量表(Quality of recovery-40 questionnaire, QoR-40)作为评估患者术后早期恢复质量的指标[9], 该量表在评估患者术后恢复质量方面较为有效可靠, 可反映各方面因素对患者术后恢复质量的影响。本文将参考 QoR-40 量表, 从患者的身体舒适度、情绪状态、神经认知功能及疼痛感受四个方面, 综述近年来艾司氯胺酮对患者术后恢复质量影响的相关研究进展, 为艾司氯胺酮未来的研究和应用提供参考。

2. 身体舒适度

2.1. 术后恶心呕吐

阿片类药物是治疗围术期疼痛的常规药物, 然而阿片类药物会导致术后恶心和呕吐(Postoperative nausea and vomiting, PONV), 使患者的住院时间延长, 增加再次住院的几率[10]。研究发现, 以艾司氯胺酮为基础的去阿片麻醉(Opioid-free anesthesia, OFA)方案可降低腹腔镜手术患者 PONV 的发生率, 这可能是因为艾司氯胺酮减少了围手术期阿片类药物的用量[11]。其他相关研究也得到了类似结果: 以艾司氯胺酮为基础的 OFA 方案能缩短妇科良性腹腔镜手术患者术后胃肠功能恢复时间, 降低 PONV 的发生率, 促进患者早日康复[12]; 脊柱融合术中, 亚麻醉剂量艾司氯胺酮联合舒芬太尼改善了患者术后疼痛, 减少了阿片类药物的需求, 减少 PONV 和胃肠道功能延迟恢复的发生, 且不影响复苏时间[13]。

2.2. 术后睡眠障碍

临床上术后睡眠障碍(Postoperative sleep disturbance, PSD)的发生率为 15%~72%, 患者主要表现为失眠、昼夜节律紊乱[14]。艾司氯胺酮具有抗抑郁作用, 可改善患有重度抑郁障碍及睡眠问题患者的睡眠障

碍[15]。一项以妇科腹腔镜手术患者 PSD 为主要研究结果的研究表明, 艾司氯胺酮显著降低了 PSD 的发生率, 且对 PSD 有预防作用, 这可能得益于艾司氯胺酮的镇痛特性、抗炎作用以及其调节昼夜节律系统方面的作用[16]。此外, 对于重症监护病房的患者, 亚麻醉剂量艾司氯胺酮能够提供较为满意的抗抑郁效果, 提高患者的睡眠质量[17]。

2.3. 术后躁动

术后躁动是患者全身麻醉后的一种常见临床表现, 可导致意外拔除静脉导管、自行拔除气管插管、术后伤口出血等不良事件, 增加了 PACU 的护理难度[18] [19]。导致全麻患者发生术后躁动的因素包括吸入麻醉药的使用、苏醒时间、手术方式、术后疼痛、低氧血症、呼吸道阻塞等[20]。其中, 术后疼痛或不适是导致术后躁动的主要因素。艾司氯胺酮可通过激活 NMDA 受体, 产生良好的镇静镇痛效果, 降低术后躁动的发生率。研究表明, 亚麻醉剂量艾司氯胺酮可在不延长拔管时间及增加术后不良作用的条件下, 减少扁桃体切除术后儿童术后躁动的发生率[21]。

3. 情绪状态

术后抑郁

近年来, 随着外科手术数量增多, 术后抑郁(Postoperative depression, POD)的发生率不断上升, 严重影响了患者的身心健康。艾司氯胺酮可持续地阻断真核细胞中的 NMDA 受体异构体和延伸因子 2 (Eukaryotic elongation factor 2, eEF2)激酶, 使 eEF2 去磷酸化, 增加原肌球蛋白受体激酶 B (Tropomyosin receptor kinase B, TrkB)的表达, 增加神经营养因子(Brain-derived neurotrophic factor, BDNF)的释放, 从而改善神经可塑性和突触形成[22], 发挥抗抑郁作用。此外, 艾司氯胺酮可以诱导雷帕霉素蛋白复合体靶标 1 (Mammalian target of rapamycin complex 1, MTORC1)信号通路和细胞外调节蛋白激酶(Extracellular signal-regulated kinases, ERK)的激活[23], 通过调节中脑多巴胺系统(D2 受体和 D3 受体)、阿片受体和单胺转运体来改善情绪[24]。临床研究表明, 艾司氯胺酮在给药 4 小时后即可产生抗抑郁作用, 且具有良好的耐受性, 单次给药后效果可持续 7 天[25]。艾司氯胺酮抗抑郁作用的具体机制在于艾司氯胺酮降低了促炎细胞因子水平以及抑制了小胶质细胞激活[26]。研究证实, 抑郁症患者内侧前额叶皮质(Medial prefrontal cortex, mPFC)中的促炎因子水平增加[27], 而促炎因子的增加进一步导致小胶质细胞激活[28]。一项以剖腹探查术术后小鼠为模型的研究同样发现, 麻醉和手术可使 mPFC 的促炎因子增加, 激活 mPFC 内的小胶质细胞, 造成白蛋白(Parvalbumin, PV)神经元丢失和神经元树突棘密度降低, 导致小鼠在术后出现抑郁样行为[29]。该项研究同时发现, 术后给予艾司氯胺酮可以逆转小鼠的神经炎症, 缓解小鼠 POD 相关异常行为, 这可能是因为艾司氯胺酮可减轻 POD 诱导的 mPFC 炎症, 减少 mPFC 中小胶质细胞的产生和激活, 对抗 POD 所致的 mPFC 中 PV 神经元的减少以及改善 POD 诱导的 mPFC 神经元树突棘的丢失等[29]。另外一项 POD 小鼠模型实验也表明, 10 mg·kg⁻¹剂量的艾司氯胺酮能够在小鼠身上产生抗抑郁作用[30]。

除降低 POD 发生率之外, 艾司氯胺酮对于改善产科患者的产后抑郁(Postpartum depression, PPD)同样有积极的作用。艾司氯胺酮复合舒芬太尼用于择期剖宫产术后患者的静脉自控镇痛, 可减少舒芬太尼用量, 改善术后镇痛效果, 减少患者产后 1 周、6 周产后抑郁发生率[3]。此外预防性使用艾司氯胺酮也可降低剖宫产患者产后抑郁的发生率[4]。

艾司氯胺酮抗抑郁作用起效较快, 静脉注射后 2 小时和 4 小时便可迅速改善抑郁症状, 且具有显著的剂量 - 反应关系[31]。艾司氯胺酮的消除半衰期仅为 1 小时至 3 小时, 但其抗抑郁作用可持续 3 至 7 天, 这可能是因为其主要代谢物去甲基氯胺酮也有抗抑郁作用[32]。

4. 神经认知功能

术后神经认知功能障碍

术后认知功能障碍(Postoperative cognitive dysfunction, POCD)是术后常见的并发症,尤其多见于老年患者,可持续至术后数周或数月,甚至数年以上,且有可能发展为永久性认知功能障碍[33]。多数 POCD 主要表现为认知能力的损害,包括记忆、情绪、精神错乱和睡眠障碍,导致恢复延迟、并发症增加和住院时间延长[34]。这些并发症会严重损害患者的个人健康,降低围术期康复质量,并对患者长期预后产生不良影响。研究表明,炎症反应是 POCD 发生和发展中的重要因素[35]。手术创伤可能会导致慢性神经炎、血脑屏障破裂、氧化应激和小胶质细胞激活等一系列反应,从而影响中枢神经系统,加剧认知功能障碍[36] [37]。老年患者因为老龄化导致促炎因子水平增加,围术期的炎症反应更加剧烈[38]。

艾司氯胺酮的抗炎特性可减少小胶质细胞的激活,下调肿瘤坏死因子- α (TNF- α)和白介素 6 (IL-6)等促炎细胞因子水平,通过调节免疫反应起到抗炎作用。临床上使用丙泊酚联合 0.5 mg·kg⁻¹ 剂量的艾司氯胺酮进行麻醉诱导,有利于减轻老年患者的应激反应,减轻炎症反应[39]。艾司氯胺酮的抗炎作用可有效降低 POCD 发生率[40]。研究发现,艾司氯胺酮可通过抑制老年小鼠中枢神经系统小胶质细胞 TLR4/NF- κ B 信号通路,降低炎症因子水平,改善神经炎症反应,从而减轻 POCD [29]。在接受部分肝切除术的老年小鼠中,术前给予亚麻醉剂量艾司氯胺酮也可下调 NF- κ B 的表达,减少炎症,从而缓解术后小鼠的认知能力下降[41]。另一项动物研究发现,除了影响经典炎症信号通路外,艾司氯胺酮可能可以通过抑制干扰素基因刺激物/TANK 结合蛋白激酶 1 (STING/TBK1)信号通路来减轻手术引起的 POCD [42]。该实验发现,剖腹探查术可导致大鼠认知记忆能力明显下降,并伴有 A2 型星形胶质细胞表型丧失,神经元 A β -42、星形胶质细胞 γ -氨基丁酸、STING 和 TBK1 等物质增加,而艾司氯胺酮可以缓解老年大鼠术后 POCD,下调神经元中 A β -42 的表达,并上调海马区中 A2 型星形胶质细胞的表达,逆转 POCD [42]。有学者认为,除抗炎作用外,艾司氯胺酮改善神经认知功能的作用可能还与其增加脑血流量、降低兴奋性递质谷氨酸浓度的作用有关[43]。

然而,目前临床上艾司氯胺酮对于预防患者 POCD 的作用仍存在争议。一项关于术中应用亚麻醉剂量艾司氯胺酮预防术后认知功能障碍的研究发现,艾司氯胺酮在预防 POCD 方面没有优势[33]。而在一些其他研究中,艾司氯胺酮与其他药物联合使用可有效减少老年患者术后炎症,预防 POCD 的发生[39];在心脏手术中,艾司氯胺酮在预防 POCD 方面具有一定的效果[44],在脊柱手术中使用艾司氯胺酮诱导和维持麻醉,同样可以促进术后认知恢复[45]。总之,艾司氯胺酮作为围术期用药是否会影响术后认知功能目前还尚未完全清楚,更多关于艾司氯胺酮与 POCD 发病机制的关系还有待研究。

5. 疼痛感受

术后疼痛

术后疼痛主要受中枢敏化、手术损伤和炎症因子的影响[46],严重影响患者的生活质量。外科手术导致的术后疼痛会引起炎症因子进一步释放,导致中枢神经系统炎症和功能障碍[38],同时也会导致阿片类药物的使用增加。不适当的术后疼痛管理会增加术后不良事件发生的风险,也是导致术后急性疼痛发展为慢性疼痛的主要危险因素[47]。因此加强围术期疼痛管理对促进患者功能恢复、减少不良反应以及提高患者总体满意度至关重要[43]。

阿片类药物是临床麻醉中最常用的镇痛类药物,可减轻术中及术后的疼痛。然而,过量的阿片类药物可能会导致呼吸抑制、痛觉过敏、药物耐受性等问题,以及产生恶心、呕吐、便秘和头晕等不良反应[38],存在一定的依赖和滥用风险[48]。多模式镇痛采用多种药物或技术相结合的方式实现麻醉镇痛,靶

向伤害性和神经病理通路中的多个受体, 缓解术后急性疼痛, 从而减少围术期阿片类药物的用量[49]。目前, 多模式镇痛逐步成为住院患者术后疼痛管理的常规方案。艾司氯胺酮作为目前唯一具有镇痛作用的静脉麻醉药, 除安全应用于临床麻醉诱导和维持外, 还可有效控制患者术后疼痛, 缓解患者负面情绪, 提高患者身体舒适度, 促进术后康复。研究发现, 艾司氯胺酮辅助阿片类药物的联合镇痛方案在不同类别手术中都取得了不错的镇痛效果。在甲状腺切除术中, 艾司氯胺酮可减少围术期舒芬太尼用量, 减轻患者术后疼痛; 在腹部手术中, 艾司氯胺酮可改善患者术后早期手术部位疼痛, 且不增加术后并发症的发生率[5]; 在腰椎融合术中, 艾司氯胺酮联合羟考酮可提供良好的术后镇痛, 减少术后羟考酮的用量, 且无明显不良反应[6]; 在剖宫产术后即刻硬膜外注入艾司氯胺酮和吗啡, 与单纯使用吗啡或单纯使用艾司氯胺酮相比镇痛效果更好[7]; 在乳腺癌术中, 艾司氯胺酮与普瑞巴林联合应用可有效改善术后急性疼痛, 预防术后慢性疼痛[8]。艾司氯胺酮联合阿片类药物可进一步减少上行伤害性传导通路的过度激活, 减少脊髓内强啡肽等引起疼痛的物质的释放[50], 有助于抑制术后急性疼痛向慢性疼痛进展[51]。然而, 也有研究发现围术期应用艾司氯胺酮并不能减少阿片类药物的使用[52] [53]。在接受妇科手术的患者中, 在切皮前和摘除子宫后给予艾司氯胺酮并不能减少吗啡的总消耗量[54]。不同研究之间的结果差异可能与研究对象、手术类别以及艾司氯胺酮的剂量和输注时间有关[55] [56]。尽管艾司氯胺酮能有效减轻术后短时间内的疼痛强度, 但可能会增加精神不良反应的发生率[13]。因此, 艾司氯胺酮在不同手术中减少阿片类药物的用量以及缓解术后疼痛的具体机制还需进一步研究。

除减少阿片类药物用量外, 艾司氯胺酮也可减少因大剂量使用阿片类药物引起的痛觉过敏的发生。阿片类药物引起的痛觉过敏是除手术刺激外影响术后疼痛的另一个外部因素[57]。瑞芬太尼引起的痛觉过敏(Remifentanyl-induced hyperalgesia, RIH)是导致患者术后慢性疼痛的危险因素之一。阿片类药物引起的痛觉过敏可能与脊髓中 NMDA 受体的表达上调导致的中枢敏化有关。中枢敏化是指在重复、恒定强度的 C 纤维刺激下, 脊髓背角神经元反应的持续时间和幅度增加的现象。NMDA 受体是神经细胞膜上的一种兴奋性谷氨酸受体, 在抗中枢敏化的发展中起着关键作用[58]。动物实验发现, 阻断 NMDA 受体可防止阿片类药物相关痛觉过敏的发展[59]。艾司氯胺酮作为 NMDA 受体拮抗剂, 可减少如 RIH 等 NMDA 受体介导的继发性痛觉过敏, 降低术后疼痛敏感性。这在临床研究中得到了验证: 在麻醉诱导前静脉注射亚麻醉剂量艾司氯胺酮可降低甲状腺手术患者疼痛敏感性[57]。

除阿片类药物的不良反应外, 围术期内患者的焦虑也是造成术后疼痛的危险因素。焦虑和疼痛往往相互交织、加剧, 使治疗和术后恢复变得更加困难[60]。研究发现, 术中输注亚麻醉剂量艾司氯胺酮可以缓解患者的焦虑, 效果可持续 3 天以上[61], 改善患者的术后疼痛。

艾司氯胺酮可在患者从麻醉中苏醒后仍然发挥特殊的镇痛作用, 甚至持续至术后数天。这种特性一方面可能是因为艾司氯胺酮的 NMDA 受体拮抗作用可在较长时间内抑制中枢敏化; 另一方面, 艾司氯胺酮在体内转化为去甲氯胺酮, 后者的麻醉效果是艾司氯胺酮的 1/5~1/3, 且消除半衰期很长[38]。

除直接缓解手术伤口疼痛外, 艾司氯胺酮对于气管插管后产生的术后咽痛也有预防作用。术前使用艾司氯胺酮含漱液能有效降低气管插管患者术后咽痛的发生率, 且无其他不良反应, 并可持续至术后 7 天以上[62]。这得益于艾司氯胺酮含漱液对口腔和上呼吸道黏膜中的 NMDA 受体和阿片受体的抑制作用以及其抗炎作用[62]。

基于以上艾司氯胺酮的镇痛特性, 目前艾司氯胺酮在去阿片麻醉(Opioid-free anesthesia, OFA)方案中也展现了一定的优势。OFA 是一种基于多模式镇痛理念的麻醉方法, 采用多种药物或技术相结合的方式实现麻醉和镇痛, 减少患者围术期的交感反射, 获得稳定的血流动力学、良好的器官灌注和高质量的麻醉恢复, 满足患者围术期的镇痛要求[63]。然而, OFA 在临床上尚未广泛应用, 其在不同类别手术中的

有效性和安全性仍然存在争议。有研究表明, 以艾司氯胺酮为基础的 OFA 可以预防术后恶心呕吐[64]。另一项研究则表明, 以艾司氯胺酮为基础的 OFA 未能降低胸腔镜手术(Video-assisted thoracoscopic surgery, VATS)患者急性疼痛的发生率, 但可减少术后轻度慢性疼痛以及不良反应的发生[65]。

6. 艾司氯胺酮不良反应

艾司氯胺酮与氯胺酮相似, 可诱发精神不良反应。患者最常见的症状是焦虑和分离, 其次是烦躁、易怒、知觉障碍、欣快感及情绪高涨等, 这可能会导致患者出现突发性精神错乱[66] [67]。意识丧失、5-羟色胺综合征等严重精神不良反应则通常多见于长期使用艾司氯胺酮的精神病患者。艾司氯胺酮对 NMDA 受体的亲和力比氯胺酮更好, 这会导致更多的精神不良反应发生[68], 成年患者尤为多见。Bowdle 等人通过招募健康志愿者组织的研究揭示了氯胺酮的迷幻效应与稳态血浆浓度之间的线性关系, 其剂量范围为 50~200 ng·mL⁻¹ [69]。这表明即使患者的血浆氯胺酮浓度已降至清醒浓度的阈值以下, 患者仍可能表现出精神症状[66]。在最常用的抗抑郁剂量(0.5 mg·kg⁻¹ 输注 40 分钟)下, 艾司氯胺酮引起的精神不良反应可持续到输注结束后 40 分钟[70]。一项针对学龄前儿童的研究发现, 艾司氯胺酮全麻诱导会增加学龄前儿童全麻术后谵妄的发生率[66]。另一项研究表明, 硬膜外麻醉下选择性剖宫产前常规预防性应用艾司氯胺酮, 97.7%的患者出现了嗜睡、眩晕及幻觉等精神症状, 67.3%的患者在手术期间出现眼球震颤, 此外术后第 1 天恶心和呕吐的发生率也较高[71]。

除精神不良反应外, 艾司氯胺酮的拟交感作用可增加成人患者的心输出量, 且呈现剂量依赖性[72]。交感神经兴奋可导致血浆去甲肾上腺素浓度增加[73], 这可能进一步导致患者出现精神不良反应。因此对于有术前高血压、严重心血管疾病、严重精神疾病和甲状腺功能亢进症的患者, 应更加谨慎应用艾司氯胺酮。艾司氯胺酮在气管插管过程中会产生急性血流动力学反应, 主要包括一过性高血压和心动过速[62]。因此在给药后需密切观察患者的心率和血压变化。然而, 也有研究表明亚麻醉剂量艾司氯胺酮对患者围术期的血流动力学影响轻微[57]。对于呼吸系统, 艾司氯胺酮具有舒张支气管的作用, 但也可使患者气道分泌物增加, 增加了麻醉诱导过程中呛咳、误吸的风险。因此需警惕患者气道分泌物的产生, 可在麻醉前给予抗胆碱类药物减少患者气道分泌物, 并在诱导过程中尽量减轻对患者气道的刺激。艾司氯胺酮还具有扩张脑血管, 升高颅内压的作用, 一般不推荐在神经外科手术中使用。此外, 艾司氯胺酮可能会影响麻醉深度的监测。研究表明, 在痔切除术中, 艾司氯胺酮患者显示出更高的围术期脑电双频指数, 并需要更大剂量的丙泊酚镇静, 这可能是造成患者延迟恢复的原因[74]。

7. 小结

艾司氯胺酮作为国内新兴的临床静脉麻醉药, 能够在保留患者自主呼吸的基础上产生镇静、镇痛作用, 在临床麻醉、围术期疼痛管理、手术室外应用、急危重症抢救与治疗等方面具有独特的价值。近年来, 针对围术期应用艾司氯胺酮的患者术后恢复质量展开了一系列研究, 尽管研究涉及的患者基础情况和临床手术类别等因素各不相同, 但研究结果均表明艾司氯胺酮良好的临床应用前景。艾司氯胺酮可以降低患者术后呕吐、术后睡眠障碍和术后躁动的发生率, 提高围术期患者的身体舒适度。艾司氯胺酮可以缓解患者的术后抑郁, 维持患者情绪状态的稳定。在术后神经认知功能障碍方面, 尽管理论上艾司氯胺酮的抗炎特性可以改善神经炎症反应, 并在小鼠实验中展现了改善术后神经认知功能障碍的潜质, 但是在临床研究中的结果存在矛盾, 艾司氯胺酮作为围手术期用药是否能改善术后认知功能尚未完全清楚。在术后疼痛方面, 艾司氯胺酮具有减少患者围术期阿片类药物用量、减轻阿片类药物相关不良反应、缓解阿片类药物导致的中枢敏化等优点, 在多模式镇痛、OFA 等技术上体现了优势, 具有一定的发展前景。综上, 可以认为围术期应用艾司氯胺酮对于改善患者术后恢复质量具有积极的作用, 这是各方面因素的

综合作用结果: 首先, 艾司氯胺酮良好的镇痛和抗抑郁作用可以提供满意的术后疼痛管理, 减轻疾病和手术创伤引起的焦虑和抑郁; 其次, 艾司氯胺酮减少术后镇痛药用量, 减少术后呕吐等不良反应的发生, 提高了患者身体舒适度和满意度[43]。

尽管艾司氯胺酮相较于氯胺酮的不良反应较轻, 临床应用时仍有诱发患者呛咳误吸、精神不良反应等风险。目前艾司氯胺酮国内应用时间较短, 仍需继续开展以国内患者为受试对象的大样本、多中心临床随机对照研究, 继续探讨艾司氯胺酮改善患者术后恢复质量方面的安全性及有效性, 拓宽艾司氯胺酮的应用领域, 为开展多模式镇痛、OFA 等技术, 为患者提供个性化药物治疗方案提供新思路。

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