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全身麻醉药物在脓毒症围术期的抗炎作用

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[摘 要] 脓毒症与机体多系统、多器官病理生理密切相关，其可致机体免疫功能紊乱，影响内环境的稳定性。脓毒症患者的麻醉风险极高。大量研究显示全身麻醉药物具有免疫调节作用，其中潜在的抗炎作用有助于减轻脓毒症引发的全身炎症反应，对脓毒症患者预后具有积极意义。因此，深入研究全身麻醉药物的抗炎作用对脓毒症患者围术期用药具有重要指导意义。

[关键词] 全身麻醉药物；围术期；脓毒症；抗炎

Anti-inflammatory effects of general anesthetics in perioperative period of sepsis

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Abstract Sepsis is closely related to the multi-system and multi-organ pathophysiology of the body, which can cause immune dysfunction and affect the stability of the internal environment. In such patients, the risk of surgery and anesthesia is extremely high. A large number of studies have shown that general anesthetics have immunomodulatory effects, and potential anti-inflammatory effects help to alleviate the systemic inflammatory response caused by sepsis, which has positive significance for the prognosis of patients with sepsis. Therefore, in-depth study of anti-inflammatory effects of anesthetics has important guiding significance for perioperative medication in patients with sepsis.

Keywords general anesthetics; perioperation; sepsis; anti-inflammatory

脓毒症是指由机体对感染的异常反应引起的威胁生命的器官功能障碍[1]。脓毒症涉及全身炎症效应、组织损伤、免疫功能障碍及毒素异常反应等多个方面，与机体多器官系统的病理生理改变密切相关。脓毒症病情危急，病死率高达30%[2]，易发展为重症脓毒症和感染性休克，许多患者常亟需外科急诊手术[3]，因此不可避免地需要使用麻醉药，这使国内外专家对脓毒症患者的麻醉部分高度重视。近年来，文献[4-8]表明部分全身麻醉药物发挥的抗炎作用对脓毒症患者有辅助治疗的意义，合理地用药更有利于指导临床围术期脓毒症患者的治疗。

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1 静脉麻醉药的抗炎作用与脓毒症

1.1 丙泊酚

丙泊酚通过抑制自身免疫系统的单核细胞和中性粒细胞功能及促炎症因子的释放，在脓毒症患者中发挥免疫调节作用。文献[9]报道：丙泊酚可以减少促炎症因子的释放，如肿瘤坏死因子α(tumor necrosis factor α，TNF-α)，白细胞介素-1(interleukin，IL-1)，IL-6，IL-8及IL-10。此外，丙泊酚被证明可减少脓毒症对部分器官的损伤。如丙泊酚可通过抑制大鼠的Toll样受体4(Toll-like receptors 4，TLR4)/核因子κB(nuclear factor κB，NF-κB)信号通路介导的诱导型一氧化氮合酶(inducible nitric oxide synthase，iNOS)、IL-6 mRNA及蛋白表达，进而抑制全身(如肝)的亚硝酸化和炎症应激，以保护大鼠免受脓毒症的损伤，从而提高生存率[10]。丙泊酚还可通过抑制缺氧诱导因子1α(hypoxia induciblefactor-1α，HIF-1α)的表达，预防脓毒症小鼠的急性肺损伤，减少脓毒症对肺的损伤[11]。此外，临床剂量的丙泊酚可通过保留和增强自然杀伤(natural killer，NK)细胞、细胞毒性T淋巴细胞的活性对免疫功能发挥保护作用[12]。

1.2 氯胺酮

氯胺酮抗炎作用的主要机制是通过抑制TLR4依赖性c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)信号通路的激活、转录因子的易位和反式激活，从而抑制脂多糖(lipopolysacchatide，LPS)活化巨噬细胞中的IL-6及TNF-α的生物合成[13]。体外研究[14-17]证明氯胺酮可通过抑制LPS激活巨噬细胞的合成，从而抑制巨噬细胞的吞噬功能及氧化能力，炎症因子mRNA的合成，以及抑制LPS产生TNF-α，IL-1b，IL-2，IL-6，从而改善盲肠结扎穿孔(cecal ligation and puncture，CLP)大鼠的术后生存率。体内研究[18-22]表明使用亚麻醉剂量的氯胺酮可使脓毒症的大鼠病死率呈现剂量依赖性降低，麻醉剂量的氯胺酮减弱了LPS诱导的肝损伤，减少了环氧合酶-2(cyclooxygenase-2，COX-2)，iNOS和NF-κB结合活性。文献[23]表明：氯胺酮是通过抑制NK细胞活性、诱导人淋巴细胞凋亡及抑制树突状细胞(DC)功能成熟而发挥免疫抑制作用。

1.3 咪达唑仑

临床剂量下咪达唑仑和丙泊酚对LPS诱导的炎症具有类似的抑制作用，但前者更为明显。若将人体的巨噬细胞暴露于含有LPS的培养基中，使用咪达唑仑后COX-2和iNOS的表达明显受到抑制[24]。此外，咪达唑仑还可以通过抑制NF-κB和JNK信号通路来抑制TNF-α，IL-1β，IL-6，IL-10等促炎症因子的产生，从而发挥抗炎特性[25]。

1.4 舒芬太尼与瑞芬太尼

Moeniralam等[26]最先在狗的脓毒症模型中发现：舒芬太尼可消除由LPS产生的TNF和IL-6对机体的不利影响，同时也可通过增加胰岛素和儿茶酚胺的水平以及抑制葡萄糖的产生来抑制血管对LPS的反应。此外，舒芬太尼可抑制NK细胞的活性发挥免疫抑制作用，同时还可降低炎症因子IL-1和IL-6的产生[27]。

在脓毒症的体内外模型中，瑞芬太尼也可通过抑制全身炎症反应而发挥作用。现有研究[28]显示：瑞芬太尼可抑制脓毒症小鼠的炎症反应、髓过氧化物酶(myeloperoxidase，MPO)的活性及iNOS的产生。瑞芬太尼通过下调NF-κB途径对促炎细胞因子(如IL-1，IL-6，TNF-α)产生抑制作用，可缓解由LPS诱导的急性肺损伤[28-30]。最近的研究[31]显示：瑞芬太尼可以通过下调蛋白激酶C(protein kinase C，PKC)βII的活化水平，来保护H9C2大鼠的心肌细胞免受LPS诱导的氧化损伤，且在LPS暴露前使用瑞芬太尼是最好的方法。目前，与舒芬太尼不同的是，临床剂量的瑞芬太尼不会损害中性粒细胞的功能，如呼吸爆发和吞噬作用，对免疫系统无明显的抑制作用[32]。

1.5 依托咪酯

较早的文献[33]记载，依托咪酯可导致急性肾上腺皮质功能不全，严重影响机体的免疫功能，极大增加ICU病死率，有数据记载使用依托咪酯与未使用的患者病死率之比为77:28。然而，近几年的研究[34-35]得出与先前相悖的结论，即单剂量依托咪酯用于重症脓毒症和脓毒性休克患者的快速诱导插管(rapid sequence intubation，RSI)中，它与病死率、血管加压素使用、ICU住院时间长短或呼吸机天数的增加之间没有关联。目前仍还没有足够的证据将依托咪酯从脓毒症患者的RSI中去除；并且现有的动物研究[36]支持依托咪酯对脓毒症大鼠的生存率无明显影响，且不加重脓毒症大鼠的肺组织炎症。相反，它可以抑制脓毒症大鼠血清中TNF-α的产生及脓毒症大鼠肾上腺细胞的凋亡。

1.6 右美托咪定

与未使用右美托咪定的患者相比，使用其作为围术期的辅助治疗药的患者体内的白细胞计数，CRP，IL-6，IL-8，IL18和TNF-α显著降低，表明右美托咪定具有一定的抗炎能力[37-39]。研究发现：右美托咪啶不仅可通过激活胆碱能抗炎途径，抑制LPS诱导的脓毒症小鼠肺组织的炎症反应[40-41]，还可通过抑制NF-κB通路从而抑制脓毒症大鼠海马的炎症反应[42]，且依赖TLR4/髓样分化因子88(myeloiddifferentiationfactor88，MyD88)/MAPKs/NF-κB信号转导途径，有效减少CLP诱导的脓毒症大鼠血浆和支气管肺泡灌洗液中炎症介质的产生[41]。最近的研究[43]显示：右美托咪定可通过增加血红素加氧酶-1的活性，抑制败血症诱发的氧化/硝化应激，并减轻败血症引起的急性肺损伤。右美托咪定在临床相关剂量下，可通过NF-κB信号通路和α2-肾上腺素能受体抑制高迁移率族蛋白B1(high mobility group protein，HMGB1)转位和HMGB1 mRNA的表达，明显降低脓毒症大鼠血液及脾组织中晚期炎症介质HMGB1含量[44]。此外，右美托咪定可通过刺激交感神经以促进淋巴细胞的凋亡，抑制免疫反应[45]。

2 吸入麻醉药的抗炎作用与脓毒症

2.1 异氟烷

据文献[46-47]记载：异氟烷可抑制脓毒症小鼠的NF-κB信号通路及iNOS/NO途径的激活，从而减少全身促炎细胞因子水平(TNF-α，IL-1，IL-6和IL-1β)和应激蛋白的相对数量、减少细胞内氧化应激活性氧(reactive oxygen species，ROS)的产生及肺损伤后肺水肿的发生等。由LPS构建的脓毒症大鼠模型中，于LPS灌注前30 min予异氟烷预处理可提高大鼠的存活率，这可能与以上的机制有关[48]。目前，虽然尚没有在人体验证异氟烷降低脓毒症机制的文献报道，但现有的文献对未来的深入研究仍具有很好的指导作用。

2.2 七氟烷

一项旨在评估使用麻醉和机械通气的猪体内自由基形成的研究和致脓毒症的大鼠CLP模型[49-50]得出七氟烷可减轻肺内炎症反应、脂质过氧化反应和氧化反应。现有文献[51]支持：七氟烷治疗后，呈现出时间依赖性减少的肺损伤的组织学征象，所有使用七氟烷处理组的ROS的产生，促炎细胞因子IL-1β、巨噬细胞炎症蛋白1(macrophage inflammatory protein 1，MIP-1)及中性粒细胞的迁移均受到抑制。其中，七氟醚是通过抑制NF-κB的激活、TLR受体介导的炎症介质表达及iNOS/NO通路等来防止血管内皮功能障碍引起的氧化应激和炎症[49,52]。目前，七氟烷已被证明在体外和体内多项研究中对LPS诱导的急性肺损伤具有保护作用[53]。此外，在脓毒症大鼠模型中，七氟醚较异氟烷更能防止CLP大鼠的脑损伤和记忆障碍[54]。因此，七氟烷可能对脏器功能的保护具有一定意义。

目前已有研究[23,55-56]发现吸入麻醉药可诱导免疫活性细胞(如NK细胞和T淋巴细胞)凋亡及肿瘤细胞产生HIF-1α，从而发挥免疫抑制作用，促进癌细胞的增殖与转移。且有学者[57]补充：与静脉麻醉药相比，吸入麻醉药的免疫抑制作用更明显，对于重症及肿瘤患者应尽可能减少吸入麻醉药的使用。

3 结语

本文系统阐述各种全身麻醉药物对脓毒症的抗炎作用，并详细介绍其潜在的抗炎机制，以求更好地指导围术期脓毒症患者的治疗。除外抗炎作用，本文还简要提出部分全身麻醉醉药物的免疫抑制作用，其中吸入麻醉药对重症患者及癌症患者产生的免疫抑制比静脉麻醉药大，因此建议该类患者可酌情选择静脉全身麻醉，减少吸入麻醉药的使用量。此外，全身麻醉药物的免疫调节作用对脓毒症的影响机制仍不完善，需要更为深入的研究来揭示二者的潜在关联，以求更透彻地了解麻醉药物，进而更有效地指导脓毒症患者的围手术期治疗。

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