

ICU 患者谵妄药物防治研究进展

何德华 王迪芬 刘旭

贵州医科大学附属医院重症医学科, 贵州贵阳 550004

通信作者: 刘旭, Email: 262347762@qq.com

【摘要】 谵妄是危重症患者常见的脑功能障碍。重症监护病房(ICU)患者谵妄发病率高达 50%~80%。谵妄的发生会导致患者机械通气时间、ICU 住院时间、总住院时间延长,病死率和医疗费用增加等,同时影响患者长期认知功能。由于谵妄发生的病理生理学机制尚不明确,目前 ICU 患者谵妄的药物防治仍处于不断探索中。常见的谵妄预防性药物有抗精神病药、右美托咪定、褪黑素、他汀类药物、氯胺酮等,但目前指南并不推荐任何一种药物预先使用来防止谵妄发生。而治疗谵妄的药物,如抗精神病药、右美托咪定、可乐定及丙戊酸钠等,存在一定的不良反应且证据不充分。目前谵妄防治缺乏明确有效的药物,仍需继续深入研究。

【关键词】 重症监护病房; 谵妄; 药物; 预防; 治疗

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Research advances in pharmacological prevention and treatment of delirium in intensive care unit patients

He Dehua, Wang Difen, Liu Xu

Department of Critical Care Medicine, the Affiliated Hospital of Guizhou Medical University, Guiyang 550004, Guizhou, China

Corresponding author: Liu Xu, Email: 262347762@qq.com

【Abstract】 Delirium is a common acute cerebral dysfunction syndrome in critically ill patients. The incidence of delirium in intensive care unit (ICU) patients is as high as 50% to 80%. Delirium can lead to prolonged mechanical ventilation, ICU and hospital stays, increased mortality, and medical costs, as well as affecting long-term cognitive function. Because the pathophysiological mechanism of delirium is unclear, pharmacological prevention and treatment of delirium in ICU patients remains to be further explored. Common prophylactic medications for delirium include antipsychotics, dexmedetomidine, melatonin, statins, ketamine, and other agents, but current guidelines do not recommend any drug for routine prophylactic use against delirium. However, drugs used to treat delirium, such as antipsychotics, dexmedetomidine, clonidine, and valproic acid, have side effects and lack sufficient evidence. Currently, research on the prevention and treatment of delirium lacks clearly effective pharmacological agents, and further in-depth investigation remains necessary.

【Key words】 Intensive care unit; Delirium; Pharmacological interventions; Prevention; Treatment

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谵妄是危重症患者的一种常见综合征,其特点是精神状态的急性变化,包括注意力不集中、思维紊乱和意识状态的改变。研究显示,普通医疗机构患者整体谵妄的发生率为 23%^[1]。重症监护病房(intensive care unit, ICU)患者的谵妄发生率为 32%,而机械通气患者约为 50%~80%^[2-4]。谵妄的危险因素包括易感因素和诱发因素,易感因素包括高龄、原有认知障碍、基础合并症及视听力障碍等;诱发因素包括疾病的严重程度、急诊或大手术、器官功能衰竭、代谢紊乱、脓毒症、机械通气、镇静镇痛等^[1]。ICU 患者因病情危重及相应的治疗干预,常合并多种谵妄危险因素,但如果没有有效的诊断工

具,谵妄将存在严重的误诊、漏诊^[5]。谵妄的识别依赖于有效的谵妄评估工具,基于广泛的验证研究,ICU 患者推荐使用两种谵妄筛查工具:ICU 意识模糊评估法(confusion assessment method for the ICU, CAM-ICU)和 ICU 谵妄筛查清单(intensive care delirium screening checklist, ICDSCL)^[6]。两种筛查工具都便于在 ICU 临床实践中实施,经过培训的临床医护人员使用时,两种筛查工具都有很高的敏感度,并可能缩短 ICU 住院时间、降低患者院内病死率^[7]。同时,新的筛查工具,如基于图表的 ICU 谵妄筛查工具(chart-based delirium detection tool for the ICU, CHART-DEL-ICU)和 CAM-ICU-7 均有助于筛

查有谵妄风险的患者并评估谵妄严重程度^[8-9]。谵妄会对ICU患者的临床救治工作造成一定干扰,如意外拔管(中心静脉导管、气管导管等)、攻击行为、不配合临床治疗等^[10-12]。因此,与非谵妄患者相比,谵妄可导致患者机械通气时间、ICU住院时间和总住院时间延长,病死率升高,医疗费用增加^[13]。此外,谵妄与出院后长达12个月的长期认知功能障碍有关,严重影响患者的日常生活^[14-17]。

鉴于谵妄短期和长期的不良预后,有效的防治手段必不可少。目前,尽管确定了许多病因,但对谵妄的病理生理学机制尚不完全清楚。现有研究表明,重症患者发生谵妄的可能机制包括:早期脑缺氧^[18];能量代谢异常导致相对的胰岛素抵抗、线粒体功能障碍和其他可能导致谵妄的代谢紊乱^[19];全身炎症使血脑屏障的通透性增加,导致中枢神经系统的炎症^[20-21];神经递质稳态失调,乙酰胆碱、多巴胺、肾上腺素和 γ -氨基丁酸(γ -aminobutyric acid, GABA)信号通路的紊乱^[22-23]。基于对谵妄病理生理学机制的认识,目前ICU患者谵妄药物防治研究也是围绕相关可能的机制开展。

1 ICU患者谵妄药物预防

1.1 抗精神病药:神经递质假说是该类药物预防谵妄研究的基础。多巴胺和血清素参与调节觉醒、运动功能和睡眠-觉醒周期,过量的多巴胺和血清素可能与谵妄有关;胆碱能系统平衡与多巴胺和血清素有关,此外,多巴胺对胆碱能系统有调节作用^[24]。第一代抗精神病药物,即典型的抗精神病药物,主要通过抑制D2-多巴胺受体来发挥作用,其中代表性的药物是氟哌啶醇^[22]。Page等^[25]发表的一项双盲随机安慰剂对照试验显示,早期使用氟哌啶醇并不能减少重症患者谵妄或昏迷时间,指出氟哌啶醇并无预防谵妄的作用。该研究共纳入141例患者,入组后给予氟哌啶醇2.5 mg或0.9%生理盐水安慰剂,每8 h静脉注射1次,研究终点为随机分组后14 d内无谵妄及无昏迷时间。结果显示,氟哌啶醇组和安慰剂组生存时间及无谵妄和昏迷时间比较差异无统计学意义。一项随机、双盲、安慰剂对照研究显示,共有1 789例重症患者预防性使用氟哌啶醇1 mg、氟哌啶醇2 mg或安慰剂;其中1 mg氟哌啶醇组因无效而提前停止;2 mg氟哌啶醇组与安慰剂组28 d中位生存时间比较差异无统计学意义;其他包括谵妄发生率、无谵妄和无昏迷时间、机械通气时间、ICU和总住院时间及不良事件发生率等次

要观察结果比较差异均无统计学意义^[26]。2025年一项纳入5个随机对照试验(randomized controlled trial, RCT)、共2 509例重症患者的贝叶斯荟萃分析显示,氟哌啶醇用于重症患者谵妄预防时,校正后的QT间期延长发生率高达65%;尽管其他安全性观察终点的风险发生概率均低于50%,但目前尚无明确临床证据支持其获益,故不推荐该药物用于此类人群的谵妄预防^[27]。

第二代非典型抗精神病药物主要是抑制D2和D3多巴胺受体,也能抑制 α 1肾上腺素能受体,并且也是五羟色胺1A受体的部分激动剂。ICU中常用的非典型抗精神病药物为奥氮平、利培酮和喹硫平。一项来自美国的小样本单中心研究表明,针对有谵妄高危因素(痴呆病史、酗酒、药物滥用)的71例重症患者,入住ICU后随机分为喹硫平预防组(12.5 mg,每日2次)和无药物预防组,喹硫平组患者谵妄发生率明显低于无药物预防组(45.5%比77.6%, $P=0.008$)^[28]。一项系统评价和荟萃分析结果显示,与安慰剂、氟哌啶醇、喹硫平等比较,奥氮平在缓解重症患者谵妄症状和缩短谵妄持续时间方面并没有优势,但接受奥氮平治疗的患者低血压发生率低于接受其他药物干预的患者,同时在入住ICU或住院时间、住院病死率和其他不良反应发生率方面差异均无统计学意义^[29]。一项多中心、安慰剂对照研究将高风险的ICU患者随机分配至氟哌啶醇组、齐拉西酮组(一种非典型抗精神病药)或安慰剂组,结果并未发现氟哌啶醇和齐拉西酮预防谵妄的证据^[30]。系统回顾和荟萃分析表明,预防性使用抗精神病药物(氟哌啶醇或非典型抗精神病药物)与谵妄的发生率、持续时间或严重程度之间无关^[31-32]。

1.2 右美托咪定:右美托咪定是一种高选择性 α 2肾上腺素受体激动剂,有轻度镇静并提供一定程度镇痛的作用。两项早期试验评估接受右美托咪定作为主要镇静药物患者的谵妄情况,结果表明,使用右美托咪定镇静的患者谵妄发生率降低^[33-34]。一项随机、双盲、安慰剂对照试验将非心脏手术后老年患者进入ICU后随机分配接受右美托咪定或安慰剂治疗,研究药物使用开始时间为术后进入ICU时,持续到术后第1天08:00。在术后前7 d,右美托咪定组谵妄发生率明显低于安慰剂组[9.1%(32/350)比22.6%(79/350),优势比(odds ratio, OR)=0.35, 95%可信区间(95% confidence interval, 95%CI)为0.22~0.54, $P<0.001$]^[35]。Skrobik等^[36]的一项有

关夜间使用右美托咪定预防 ICU 谵妄的试验结果表明,在原有镇静水平上夜间添加低剂量的右美托咪定(剂量减少 50%),患者的谵妄发生率明显降低(20% 比 46%, $P=0.006$)。一项在 8 个国家、74 个 ICU 中开展的临床研究中,4 000 例机械通气患者被随机分为接受右美托咪定组或常规治疗组(主要是丙泊酚),常规治疗组与右美托咪定组谵妄发生情况与 90 d 病死率比较差异均无统计学意义^[37]。一项多中心研究中,432 例脓毒症患者随机接受右美托咪定或丙泊酚作为主要镇静剂,结果显示,右美托咪定组和丙泊酚组无谵妄或昏迷时间比较差异均无统计学意义^[38]。然而,在上述两项临床研究中,使用右美托咪定镇静的患者有更多的不良事件,包括贲门弛缓、低血压和自行拔管等。Lewis 等^[39]的一项包括 77 项临床 RCT 的系统评价和荟萃分析显示,在机械通气成人患者中,使用右美托咪定和其他镇静剂(丙泊酚、咪达唑仑等)比较,谵妄的风险较低,机械通气和 ICU 住院时间缩短,但增加了心动过缓和低血压的风险。

1.3 褪黑素:褪黑素是松果体中产生的一种激素,生理功能为维持昼夜节律,此外,褪黑素还有抗氧化和抗炎特性,可用于改善睡眠障碍^[40]。昼夜节律失调、睡眠剥夺是导致 ICU 患者谵妄的原因之一^[41]。研究表明,重症患者的褪黑素水平非常低^[42-43]。因此,褪黑素的应用可能是避免 ICU 患者发生谵妄的有效措施。一项临床试验以双盲方式随机选择患者在 ICU 住院期间每天 21:00 接受 3 mg 褪黑素或安慰剂,结果显示,褪黑素组谵妄发生率明显低于对照组(51% 比 85%, $P<0.001$),褪黑素组谵妄持续时间也较对照组明显缩短($d:6$ 比 9 , $P=0.001$)^[44]。在一项更大的双盲随机试验中,患者随机每晚给予 10 mg 褪黑素或安慰剂,结果显示,褪黑素组的睡眠质量较安慰剂组明显改善,但谵妄情况并没有明显改善^[45]。Wibrow 等^[46]的一项临床研究结果表明,入住 ICU 48 h,连续 14 d 或转出 ICU 前,每晚 21:00 肠内给予褪黑素或安慰剂,两组患者谵妄发生率比较差异无统计学意义。一项纳入 9 项 RCT、1 625 例重症患者的荟萃分析表明,使用褪黑素/雷美替胺(褪黑素受体 M1 及 M2 激动剂)预防 ICU 谵妄,与安慰剂组比较,使用褪黑素/雷美替胺并没有降低谵妄发生的风险[风险比(risk ratios, RR)=0.76, 95%CI 为 0.54~1.07, $P=0.12$, $I^2=64\%$],同时对机械通气时间、ICU 住院时间以及病死率也无改善作

用^[47]。然而,因为纳入的 RCT 所使用的褪黑素剂量及给药时间均有较大异质性,因此针对褪黑素预防 ICU 谵妄的作用,如何选择更为合理的给药方案是进一步研究的方向。一项多中心适应性 RCT 比较低剂量褪黑素(每晚 0.3 mg)、大剂量褪黑素(每晚 3 mg)与安慰剂对 ICU 机械通气患者谵妄预防作用的结果显示,低剂量褪黑素的药代动力学更优,但所有剂量均未降低谵妄发生率,相关次要结局比较差异也无统计学意义^[48]。

1.4 他汀类:他汀类药物是一种羟甲基戊二酸单酰辅酶 A(3-hydroxy-3-methylglutarate monoacyl coenzyme A, HMG-CoA)还原酶抑制剂,主要用于治疗高胆固醇血症和改善心血管状况,同时也具有抗炎特性^[49]。由于神经炎症是诱发谵妄的可能机制,研究人员认为它的抗炎特性可能是减少神经炎症,从而减少危重患者的谵妄^[50]。早期研究表明,在危重患者中使用他汀类药物可能会减少谵妄的发生^[51-52]。但两项大型 RCT 并没有发现类似结果。一项评估瑞舒伐他汀对急性呼吸窘迫综合征患者病死率影响的辅助研究表明,瑞舒伐他汀组和安慰剂组谵妄时间占比比较差异无统计学意义(34% 比 30%, $P=0.22$)^[53]。一项比较机械通气患者随机接受辛伐他汀或安慰剂的临床研究显示,辛伐他汀组和安慰剂组无谵妄和昏迷时间比较差异无统计学意义($d:5.7$ 比 6.1 , $P=0.66$)^[54]。Vallabhajosyula 等^[55]的一项系统回顾分析显示,住院前服用和未服用他汀类药物患者出现谵妄风险差异无统计学意义。

1.5 氯胺酮:氯胺酮是一种非竞争性 N-甲基-D-天门冬氨酸(N-methyl-d-aspartate, NMDA)受体拮抗剂,可用于诱导麻醉和 ICU 镇静^[56]。此外,氯胺酮还有其他多种作用,且部分呈剂量依赖性,包括阿片受体阻断、GABA 抑制、多种抗炎特性,以及对单胺的释放和再摄取的影响,包括去甲肾上腺素、5-羟色胺和多巴胺^[57]。将氯胺酮作为镇痛剂使用时,可能会减少谵妄的发生。一项单中心、探索性临床试验在麻醉诱导期间随机给予心脏手术患者氯胺酮(单次剂量 0.5 mg/kg 静脉注射)或安慰剂,结果显示,与安慰剂组比较,氯胺酮组谵妄发生率明显降低(3% 比 31%, $P=0.01$)^[58]。然而,一项国际多中心双盲试验显示,单次剂量氯胺酮并不能改善谵妄发生率,但可能增加幻觉、噩梦等的发生率^[59]。另外一项单中心双盲随机对照试验结果表明,与安慰剂比较,连续接受氯胺酮治疗的患者谵妄发生率

更低,谵妄持续时间更短^[60]。目前有关氯胺酮预防ICU谵妄的作用尚无一致的结论,正在进行的镇痛-镇静辅助药物氯胺酮用于机械通气ICU患者(the analgo-sedative adjunct ketamine infusion in mechanically ventilated ICU patients, ATTAINTMENT)试验^[61]可能有助于进一步阐明氯胺酮和谵妄之间的关系。

2 ICU患者谵妄的药物治疗

2.1 抗精神病药:抗精神病药物有镇静作用,在一段时间内,氟哌啶醇被推荐为谵妄的一线治疗药物。但近年来,大型多中心RCT并没有表明使用氟哌啶醇治疗能使ICU谵妄患者获益。一项多中心、随机、安慰剂对照研究比较了566例急性呼吸衰竭或休克患者使用氟哌啶醇、齐拉西酮和安慰剂治疗谵妄的情况,结果显示,安慰剂组调整后的中位无谵妄或昏迷生存时间为8.5 d(95%CI为5.6~9.9),而氟哌啶醇组为7.9 d(95%CI为4.4~9.6),齐拉西酮组为8.7 d(95%CI为5.9~10.0), $P=0.26$;与安慰剂组比较,各组机械通气、入住ICU或住院时间、ICU再入院时间、30 d或90 d病死率比较差异无统计学意义^[3]。Andersen-Ranberg等^[62]进行的氟哌啶醇治疗ICU谵妄的临床试验将1 000例患者随机分为氟哌啶醇组(510例)和安慰剂组(490例),结果显示,氟哌啶醇组平均生存时间[35.8 d(95%CI为32.9~38.6)]与安慰剂组[32.9 d(95%CI为29.9~35.8)]比较差异无统计学意义($P=0.22$);氟哌啶醇组90 d病死率较安慰剂组有降低趋势(36.6%比43.3%)。一项纳入7项RCT、1 767例重症患者的贝叶斯荟萃分析显示,氟哌啶醇可降低ICU谵妄患者的全因病死亡率,减少苯二氮草类药物的使用;同时,氟哌啶醇导致严重不良事件的临床重要危害概率仅为2%。其中,校正后的QT间期延长、锥体外系反应等其他安全性终点的临床重要危害,其贝叶斯后验概率均低于50%。这表明氟哌啶醇的整体风险可控^[26]。因此,氟哌啶醇治疗谵妄对ICU中的一部分患者可能是安全和有益的,未来研究应进一步明确氟哌啶醇可能受益的患者。

2.2 右美托咪定:关于右美托咪定在降低谵妄发病率及缩短其持续时间方面的作用,已有广泛的研究报告。一项多中心、双盲、安慰剂对照RCT评估了右美托咪定对于改善躁动型谵妄机械通气患者的作用,结果显示,与安慰剂组比较,右美托咪定组中位谵妄恢复时间明显缩短[h:23.3(13.0, 54.0)

比40.0(25.3, 76.0), $P=0.010$];同时,安慰剂组接受抗精神病药物(氟哌啶醇、利培酮、奥氮平或喹硫平)治疗患者的比例明显高于右美托咪定组(65.6%比36.8%, $P=0.020$),7 d中位无呼吸机时间明显延长[h:144.8(114.0, 156.0)比127.5(92.0, 142.8), $P=0.010$],中位拔管时间明显缩短[h:21.9(18.3, 27.7)比44.3(25.3, 94.2), $P<0.001$]^[63]。尽管这项试验表明,右美托咪定有改善躁动型谵妄机械通气患者临床症状的作用,但由于样本量过少,仍需进行确认性试验。本课题组前期的一项包含15项RCT的系统评价和荟萃分析显示,重症谵妄患者采用右美托咪定治疗后可降低谵妄发生率($OR=0.39$, 95%CI为0.20~0.76, $P=0.006$)、缩短谵妄恢复时间(95%CI为-45.28~-1.21, $P=0.04$);但右美托咪定可能面临更高的心动过缓风险($OR=3.48$, 95%CI为1.47~8.23, $P=0.004$)^[64]。一项多中心、双盲、安慰剂RCT显示,与安慰剂相比,右美托咪定治疗非插管ICU躁动型谵妄患者能明显缩短躁动持续时间,复合终点更优,且安全性相当^[65]。然而,该研究因中期分析有效而提前终止,存在效果高估可能,且样本有限。因此,右美托咪定可作为该类患者躁动控制的可选方案,但结论需进一步验证。

2.3 可乐定:可乐定是一种 α_2 肾上腺素能激动剂,与右美托咪定类似,能降低中枢神经系统的交感神经张力,并提供镇痛作用。一项安慰剂RCT结果显示,接受急性主动脉夹层手术的患者,可乐定组术后谵妄程度较低^[66]。一项对3 614例危重患者谵妄的大型前瞻性观察研究结果表明,与未经治疗的谵妄患者比较,接受可乐定治疗的谵妄患者谵妄更难解决($OR=0.78$, 95%CI为0.63~0.97);同时患者谵妄持续时间、机械通气时间、ICU住院时间及总住院时间均延长^[67]。

2.4 丙戊酸钠:丙戊酸钠是一种抗癫痫药/心境稳定剂,主要是增强GABA神经传导,其次是阻断电压依赖性钠通道;此外,该药物还可能有抗炎特性,并能阻断谷氨酸和NMDA^[68]。一项回顾性分析表明,接受丙戊酸钠单药治疗的患者比接受丙戊酸加抗精神病药物治疗的患者更容易解决躁动和谵妄问题^[69]。鉴于该研究会受到选择偏差的干扰,针对丙戊酸治疗ICU患者谵妄的作用仍需进一步的RCT进行明确。

3 总结与展望

由于谵妄发生的病理生理学机制尚不明确,目

前 ICU 患者谵妄的药物防治仍处于不断地探索当中,指南也不推荐任何一种药物预先使用来防止谵妄发生。谵妄由于类型众多,在发生发展过程中存在高度可变性,谵妄的预防和治疗经常存在重叠现象。目前治疗谵妄的药物多具有镇静作用,在躁动型谵妄患者中固然可选择使用相关药物来控制患者的过度活跃行为,但有关 ICU 患者谵妄的药物治疗也仍需进一步探索。

鉴于缺乏谵妄防治的有效药物,谵妄防治管理应侧重于尽量减少危险因素,同时积极实施非药物干预;循证医学证据表明 ICU 患者 ABCDEF(A 为评估、预防和管理疼痛, B 为自主清醒试验和自主呼吸试验, C 为镇痛和镇静的选择, D 为谵妄评估、预防和管理, E 为早期运动和锻炼, F 为家庭参与)集束化管理可能是行之有效的措施。与此同时,进一步加强有关阐明谵妄发病机制的基础和转化研究可能有助于更好地指导 ICU 患者谵妄的管理。

利益冲突 所有作者均声明不存在利益冲突

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