

腹部手术后谵妄的研究进展

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■背景资料

术后谵妄(postoperative delirium, POD)是腹部手术后常见的急性综合征, 准确的诊断及正确的处理是改善预后的关键。POD的发生与患者术前存在的基础疾病及围手术期的药物使用密切相关, 但具体的发生机制尚不明确, 目前认为主要由乙酰胆碱等神经递质的缺乏所导致。非药物性手段在POD防治中因表现出了一定的优势而逐渐受到关注。

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Recent progress in research of postoperative delirium after abdominal surgery

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Abstract

Postoperative delirium (POD) is a common acute cerebral syndrome after abdominal surgery, with disturbance of consciousness, cognition and attention as the main clinical manifestations, found mostly in elderly male patients. POD often increases mortality dramatically and prolongs the length of hospital stay. There are many factors responsible for the occurrence of POD, such as age, underlying diseases and antipsychotic drugs. Due to the complex onset of the disease, multicomponent intervention strategies have been recommended and proved effective. In contrast, there has been no evidence that pharmacological prevention or therapy could reduce the incidence or shorten the duration of POD. This paper reviews the recent progress in research of

postoperative delirium after abdominal surgery with regards to its mechanism, risk factors, prevention and treatment.

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Key Words: Postoperative delirium; Abdominal surgery

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摘要

术后谵妄(postoperative delirium, POD)是腹部外科手术后一种常见的急性综合征, 以意识、认知障碍及注意力不集中为主要临床表现。围手术期谵妄以老年男性多见, 一旦发生会提高患者的死亡率, 延长住院时间并增加住院费用。有多种原因参与POD的发生, 包括患者高龄、术前存在的基础性疾病及麻醉镇静药物使用等。就治疗方面来讲, 过去主张使用氟哌啶醇等药物性治疗, 但最新的研究表明, 非药物手段的多元化介入策略(multicomponent intervention strategies)在临床试验中表现出了预防和治疗优势, 并逐渐被业界接受。本文主要就腹部外科手术后POD的影响因素、预防和治疗的最新进展作一综述。

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关键词: 术后谵妄; 腹部手术

核心提示: 术后谵妄(postoperative delirium, POD)是腹部手术后常见的急性综合征, 增加患者的住院时间及死亡风险, 本文就腹部POD的发生原因、机制及诊治进展进行了综述, 对临床工作提供一定的帮助。

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0 引言

术后谵妄(postoperative delirium, POD)指术后数天内发生的一种可逆的急性波动性精神紊乱综合征, 包括了意识、认知、注意力、记忆、定向及运动行为方面的紊乱。谵妄是一种常见的临床表现, 2012年据世界卫生组织(World Health Organization, WHO)统计, 欧洲住院老年患者谵妄发生率50%^[1]。随着谵妄的发生, 伴随而来的是患者死亡率升高, 住院时间延长及住院花费增加, 而由于手术创伤的打击加之围手术期生理精神因素的改变, 谵妄发生率和死亡率分别可达37%-74%和20%^[2], 曹建国等^[3]统计380例65岁以上住院手术患者中, 135例非心脏手术患者POD占29.6%, 其中普外科腹部手术后发生率为38%。因此普外科医生了解POD, 及时发现并采取有效措施是十分必要的。本文就近年来腹部手术POD的发生机制、影响因素及其诊治的最新进展作一综述。

1 临床诊断及诊断工具

1.1 症状及诊断标准 患者常在术后第1-3天急性或亚急性发作且病情波动, 表现为注意力不集中、意识障碍、认知障碍(包括定向障碍、记忆障碍、语言改变), 其他表现包括睡眠-觉醒周期紊乱, 幻觉、错觉、精神运动障碍, 不良行为、情绪不稳定。临床观察到的谵妄患者通常表现为烦躁不安, 但也可表现得异常安静, 由此分为兴奋型和沉默型。患者症状常在夜晚加重, 称为日落现象, 意识方面出现昏睡或觉醒过度, 定向(人、空间、时间)障碍表现为不识来人、亲友, 错觉和幻觉是认知障碍的表现, 许多患者的被害妄想逼真, 导致他们易激惹、躁动甚至产生攻击行为。另外, 患者短期记忆受损, 呈现逆行性遗忘。沉默型患者出现情绪混乱, 可表现为严重抑郁的情感淡漠, 也可以是严重的恐慌和焦虑。

谵妄诊断确立之后, 关键需要找出导致谵妄的原因, 腹部外科大手术后身体内环境发生改变, 如感染、低血糖、电解质紊乱、脱水等, 加之镇痛不足、抗胆碱能药物、镇静止痛药物过量等是引发POD的常见原因, 还需注意肝胰手术后出现的肝性脑病、胰性脑病以及术后长期肠外营养导致的维生素B1缺乏性Wernicke脑病。

因此谵妄出现后应积极进行血生化、脑影像[计算机断层扫描(computed tomography, CT)、磁共振成像(magnetic resonance imaging, MRI)]等检查。目前应用最广泛的两种谵妄诊断标准是WHO制定的国际疾病分类第10版(ICD-10 1993年)^[4]和美国精神医学学会出版的精神障碍诊断与统计手册第5版(DSM-5 2013年)^[5]。前者的诊断标准中有睡眠-觉醒周期紊乱一项, 而后者更注重相似疾病之间的鉴别, 例如有痴呆病史、药物或酒精所致的戒断作用间的区别, 且诊断标准少, 应用更加简单。

1.2 诊断工具 诊断工具的使用提高了临床诊疗工作效率, 目前有超过24种谵妄诊疗工具, 最为广泛使用的是Inouye等以DSM-III-R为标准制定的谵妄评定方法(confusion assessment method, CAM)^[6-8], Wei等^[9]在对1000余例患者进行系统回顾中证实了其有效性, 其中敏感性为94%, 特异性89%, 评定者间信度高。谵妄评定方法包括4项内容: (1)急性发作和波动病程: 患者精神状态在短时间有无明显改变, 1 d之内行为是否波动(症状出现或消失, 加重或减弱); (2)注意力不集中: 注意力难以集中, 容易分散; (3)思维混乱: 谈话主题散漫, 思维不清晰或不合逻辑, 或从一个主题不可预测地跳到另一个主题; (4)意识改变: 患者意识是否表现为警醒、嗜睡、昏睡或昏迷。当(1)和(2)共同具备, 再加上(3)或(4)中的任意一项, 即可诊断谵妄。

2 病理生理学

谵妄发生机制学说众多, 但确切机制尚不明确, 大部分理论都不能单独解释POD, 理论之间互相有关联。但所有研究表明最后都与神经递质的合成及功能紊乱有关, 从而导致了行为及认知的改变。神经递质紊乱中最多见的是乙酰胆碱缺乏及多巴胺过多, 或由抗胆碱药物和拟多巴胺药物使用带来的不良影响^[10]。以下列举目前最有影响的几种学说:

2.1 神经炎症(neuroinflammatory)学说 包括由外周部位感染和全身性炎症反应引起的神经炎症^[11]。有确切证据表明急性全身性炎症与谵妄之间存在关系^[12,13], 当发生系统炎症、缺氧或者疼痛时, 血脑屏障通透性增加, 循环血液中的细胞、炎症因子或者神经兴奋性药物如阿片类代谢产物可透过屏障进入中枢^[14,15]。受此影响, 中枢本身会产生炎症介质, 并随着炎症反应的发生, 依次产生神经递质紊乱, 神经内分泌改变,

■ 研发前沿

目前手POD的非药物性预防和治疗是本领域的研究热点, 其主要手段是针对围手术期导致谵妄的多种诱因和易感因素进行干预, 因此后续研究应针对非药物防治方法进行改进, 使其更加符合现实临床需求。

■相关报道

Inouye等对谵妄进行了长期的研究,并报道了HELP(hospital elder life program)法作为一种非药物性防治手段被应用于临床,而由此法衍生出的一系列改进方法也见诸于文献报道中。

神经功能失调甚至神经细胞死亡,最终导致临床症状^[16-18]。

2.2 神经细胞老化(neuronal aging)学说 在对老年人及术前痴呆患者大脑的研究中发现,由于大脑的形态及功能学改变使得在系统性炎症反应下具有更高的发病率。乙酰胆碱能抑制小神经胶质细胞的活性,老龄人和痴呆患者大脑乙酰胆碱相对缺乏,加之抗胆碱类药物使用,造成小神经胶质细胞过分活跃^[16],活化的小神经胶质细胞是中枢系统的免疫效应细胞,过度活化造成自身细胞的免疫损伤,由此不仅能解释这些患者的POD高发生率,还能解释谵妄病程中顽固性的症状,如进行性神经炎症、神经退行性病变^[18]。

2.3 氧化应激反应(oxidative stress)学说 手术以后人体血流动力学发生改变,机体代谢增加造成颅内血氧、灌注率下降。而缺氧、细胞膜ATP泵供能不足,使细胞内电解质浓缩,如胞内高钙离子,导致神经元功能失调。此外,氧化应激引起某些神经递质代谢紊乱,如谷氨酸、多巴胺和去甲肾上腺素合成增多,乙酰胆碱合成减弱^[17]。

2.4 神经递质缺乏(neurotransmitter deficiency)学说 之前已述氧化应激反应会减少乙酰胆碱,与POD相关的神经介质以及抑制性神经介质 γ -氨基丁酸(γ -aminobutyric acid, GABA)和5-羟色胺(5-hydroxy tryptamine, 5-HT)^[17,19,20]。乙酰胆碱在维持意识清醒、注意力和学习记忆中的作用非常关键,通常认为其缺乏是谵妄发病最后的共同通路,他的不足常常与多巴胺的过量相关^[19,20]。虽然乙酰胆碱不足与谵妄相关,但是乙酰胆碱酯酶抑制剂对谵妄无明显治疗及预防效果^[21-23]。

3 相关的因素

虽然POD发生的病理生理学机制尚不明了,但业界逐渐接受的是,其发病由多种易感因素与诱发因素之间共同作用引起的。

3.1 易感因素(predisposing factors) (1)年龄 ≥ 75 岁; (2)基础疾病史,术前房颤;外周血管疾病;心脑血管疾病史;肾功能不全;糖尿病(尤其是血糖控制不良者); (3)术前存在认知障碍^[24],如痴呆; (4)术前听力、视觉损伤; (5)既往谵妄病史^[25]; (6)酗酒^[26,27]; (7)术前营养不良(血清总蛋白 < 30 g/L)及电解质紊乱^[28-30]; (8)术前贫血; (9)抑郁症病史^[31]; (10)躁郁症或精神分裂症是独立危险因素^[32]。

3.2 诱发因素(precipitating factors) (1)有创检查

或手术^[33]; (2)部分麻醉药物的使用,如术中使用长效阿片类药物对比短效制剂风险更大;围手术期使用芬太尼的剂量与发病成正比^[34,35]; (3)苯二氮卓类药物是发病的独立因素; (4)抗胆碱类药物或具有抗胆碱/抗组胺不良反应药物^[36]; (5)术中低血压^[37]; (6)术后48 h内缺氧是独立危险因素^[38]; (7)术后镇痛不足^[39]; (8)术后心输出量低; (9)急性出血性贫血、输血增加风险,且发生率与严重程度与输血量呈正相关^[40]; (10)术后急性肾衰^[41]; (11)围手术期感染,血清中炎症因子如白介素-6(interleukin 6, IL-6)、IL-8、C反应蛋白(C reactive protein, CRP)与发生率、严重程度、持续时间密切相关^[42,43]; (12)重症监护病房(intensive care unit, ICU)患者的谵妄发生率明显提高:导尿、限制活动(身体制动)、睡眠不足、昼夜节律紊乱^[44,45]。患者进入ICU后会导致紧张情绪,血清皮质醇水平上升^[46]; (13)呼吸机的长时间使用,其使用时间与发病率及使用时间呈正相关^[47]; (14)围手术期神经学合并症,如脑缺血、脑出血^[48]。

4 预防和治疗

4.1 非药物性预防和治疗 积极发现术前易感因素及避免诱因可以更好地针对性预防和治疗POD。控制单一的风险因素或许不足以改善谵妄发生与病情,多元化策略才是最有效针对预防与治疗的手段。

作为一种非药物手段,多元化介入策略(multicomponent intervention strategies, MIS)因在POD的预防与治疗中表现出的优势^[49,50],已逐渐被业界所接受,并列入到英国国家优化卫生与保健研究所(National Institute for Health and Clinical Excellence, NICE)指南当中^[6]。MIS针对围手术期多项诱因和易感因素进行干预。护理方面,鼓励患者术前进行适度身体锻炼,术后尽早活动,尽量避免导尿;帮助患者恢复定向障碍;给视觉或听觉障碍的患者佩戴眼镜、助听器;提高睡眠质量,有条件可给高风险及已患病患者提供单间,避免夜间护理和治疗项目;治疗方面,应有效缓解疼痛,积极纠正贫血,低血氧,低/高血压,保证足够碳水化合物及其他营养物质摄入;精神兴奋药物的使用及有创操作均为诱发因素,应尽量避免。在多元化介入策略中,应用最广泛的是由美国Inouye教授提出的HELP(hospital elder life program)法,目前已被全球超过200家医院使用,并衍生出了一系列改

进方法^[51]。Chen等^[52]在一项前瞻性研究中观察了HELP改进法对腹部外科手POD发生率的影响, 其中实验组($n = 102$)和使用常规护理方法的对照组($n = 77$)POD的发病率分别为0.0%和16.7%($P < 0.001$)。

虽然MIS能降低POD发病率, 但或许不是其中的每一项干预方法都是有效可行的。Jeffs等^[53]就得出了阴性结果, 他们将649例入院时无谵妄的内科老年患者(≥ 65 岁)纳入研究, 实验组对患者定向力、活动两项内容进行干预($n = 305$), 对照组行常规护理($n = 344$), 结果显示, 住院期间谵妄在实验组发生率4.9%(15/305, 95%CI: 2.3-7.3), 对照组为5.9%(20/339, 95%CI: 3.8-9.2), 两组间差异无统计学意义($\chi^2 = 0.301$; $P > 0.05$)。需要指出的是, 这项研究只针对内科患者进行了定向和活动干预, 并不能否认MIS的有效性, 能否完善MIS, 使其满足临床的不同需求, 有待进行更多的研究。

4.2 药物性预防和治疗 一代抗精神病药物如氟哌啶醇过去被用于POD治疗, 但在氟哌啶醇与二代抗精神病药对比研究中, 前者对谵妄持续时间和严重程度的影响并无优势, 而使用后可能出现锥体外系症状^[54-57], 因此不被建议用于POD。最近的一些研究结果也不支持氟哌啶醇的使用, Fukata等^[58]将119例拟择期行腹部手术或骨科手术患者(≥ 75 岁)纳入研究, 术后前3 d给予小剂量氟哌啶醇, 观察术后7 d内谵妄发生情况, 结果在实验组($n = 59$)和对照组(使用安慰剂; $n = 60$)中发病率分别为42.4%和33.3%, 差异无统计学意义($P = 0.309$), 且发病的严重程度也未见改善。同样的, 在ICU和老年患者的应用中, 氟哌啶醇组的发病率和持续时间和使用安慰剂的对照组差异均无统计学意义^[59-61]。

目前, 右旋美托咪啶治疗谵妄的效果较为肯定, 持续静脉输注可以减少谵妄的持续时间, 术中用于镇静可降低POD发病率, 他的这种作用或许与其对胆碱能和GABA能系统影响较小且促进正常睡眠结构有关^[62-64], 因此被美国重症医学会(Society of Critical Care Medicine, SCCM)2013年指南推荐使用^[65]。同被推荐的还有二代抗精神病药, 而苯二氮卓类药物因可能诱发谵妄, 故不建议使用。睡眠的不足是危险因素之一, 应用褪黑素也可预防性的减少POD的发生^[66]。另外, 乙酰胆碱的缺乏是POD关键的发生机制, 但实际上, 胆碱酯酶抑制剂如利斯的明并无预防效果^[67,68]。最近的研究^[69]报道, 麻醉中

使用小剂量的氯胺酮可能减少术后疼痛、预防POD的发病, 但是这一信息还未被证实, 一项大型临床研究正在进行中。

5 结论

谵妄是腹部外科手术术后常见的疾病, 增加患者死亡率, 延长住院时间, 增加住院费用。外科医生通常对POD缺乏足够的认识, 容易与一些功能性神经障碍相混淆, 有时单纯地认为是麻醉后遗症而未引起重视。因此, 有效预防及治疗POD对医生提出了更高的要求。降低POD的发生及严重程度主要依靠医护人员提高对疾病以及易感、诱发因素的认识, 针对高危患者进行风险评估, 采取预防措施, 在疾病发生之后积极进行治疗, 另一方面, 需要患者家属的积极配合。同时, 外科医生限于本专业的知识范围, 应及时与相关科室沟通, 多学科之间合作。

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■创新盘点

本文详细介绍了近年来对腹部手POD发生机制、原因及治疗的研究进展。

■应用要点

本文重点阐述了腹部POD发生的相关因素及防治进展,相信对临床中避免POD的发生、及时有效的发现和治疗会带来帮助。

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同行评价

本文综述了腹部 POD 的发生原因及诊疗进展, 针对临床常见问题提出诊疗思路, 对临床治疗具有指导意义。

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