ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2024 年 2 月 28 日　第 32 卷　第 2 期　(Volume 32 Number 2)

2/2024

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

ISSN 1009-3079
9 771009 307056 02>

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编务 张砚梁; 送审编辑 张砚梁; 组版编辑 张砚梁; 英文编辑 王天奇;
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世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名
(月刊)

创　刊 1993-01-15
改　刊 1998-01-25
出　版 2024-02-28
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

编辑部
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《世界华人消化杂志》编辑部
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

制作
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《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

定价
每期136.00元 全年12期1632.00元

WCJD 世界华人消化杂志®

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Volume 32 Number 2 February 28, 2024

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date February 28, 2024

NAME OF JOURNAL
World Chinese Journal of Digestology

ISSN
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Chinese Journal of Digestology
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
https://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PRODUCTION CENTER
Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381901

PRINT SUBSCRIPTION
RMB 136 Yuan for each issue
RMB 1632 Yuan for one year

INSTRUCTIONS TO AUTHORS
Full instructions are available online at https://www.wjgnet.com/1009-3079/Nav/36. If you do not have web access, please contact the editorial office.

WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2024年2月28日; 32(2): 97-101

DOI: 10.11569/wcjd.v32.i2.97

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

中重型颅脑损伤患者继发应激性溃疡机制和防治策略研究进展

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收稿日期: 2023-12-04
修回日期: 2023-12-20
接受日期: 2024-01-11
在线出版日期: 2024-02-28

Pathogenic mechanism and preventive and therapeutic strategies for secondary stress ulcers in patients with moderate to severe traumatic brain injury

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Received: 2023-12-04
Revised: 2023-12-20
Accepted: 2024-01-11
Published online: 2024-02-28

Abstract

Moderate to severe traumatic brain injury is a complex and critical clinical disease, which is prone to secondary stress ulcers (SU). The pathogenic mechanism of secondary stress ulcers in moderate to severe traumatic brain injury is complex and often related to increased intracranial pressure, excitation of the vagus nerve, increased secretion of catecholamines, decreased gastric mucosal perfusion, and H+ reverse osmosis. While treating traumatic brain injury, actively preventing stress ulcers is the key to improving patient prognosis. Proton pump inhibitors (PPIs) and histamine receptor 2 antagonists (H2RAs) are widely used in the prevention and treatment of stress ulcers, but their preventive effects and drug side effects are still controversial. The occurrence of stress ulcers is a result of multiple factors. Previous research has provided certain reference value for clinical practice, but it is difficult to accurately guide the scientific prevention and treatment of stress ulcers in clinical practice. In the future, evidence-based medicine should be used to develop guidelines for the prevention and treatment of stress ulcers, clarify the timing of intervention, define indications for preventive medication, and formulate standardized treatment.

Key Words: Traumatic brain injury; Stress ulcer; Pathogenesis; Preventive and therapeutic strategies

Citation: Cheng J, Cai LY, Tang QQ. Pathogenic mechanism and preventive and therapeutic strategies for secondary stress ulcers in patients with moderate to severe traumatic brain injury. Shijie Huaren Xiaohua Zazhi 2024; 32(2): 97-101
URL: https://www.wjgnet.com/1009-3079/full/v32/i2/97.htm
DOI: https://dx.doi.org/10.11569/wcjd.v32.i2.97

摘要

中重型颅脑损伤是复杂的危重临床疾病, 容易继发应激性溃疡(stress ulcer, SU)值得关注. 中重型颅脑损伤继发应激性溃疡的机制复杂, 多与颅内压增高, 迷走神经兴奋, 儿茶酚胺分泌增多, 胃黏膜灌注减少, H+逆向渗透有关. 治疗颅脑损伤的同时, 积极预防应激性溃疡是改善患者预后的关键. 质子泵抑制剂(proton pump inhibitor, PPI)、组胺受体拮抗剂(histamine H2 receptor antagonists, H2RA)被广泛应用于应激性溃疡的预防和治疗, 但是其预防效果和药物副作用方面还存在较大争议. 应激性溃疡的发生涉及多种因素的综合作用, 既往研究为临床提供了一定的参考价值, 但是很难精准地指导临床应激性溃疡的科学防治, 未来应依据大量循证医学证据制定应激性溃疡防治指南, 明确干预时机, 预防性用药适应症, 形成规范化治疗.

关键词: 颅脑损伤; 应激性溃疡; 发病机制; 防治策略

核心提要: 颅脑损伤后发生应激性溃疡是由于神经体液调节与内分泌失衡多种因素综合作用. 胃黏膜屏障破坏是颅脑损伤后应激性溃疡病变形成的基础, 胃酸分泌增多和胃蛋白酶的侵袭作用促进病变发展. 颅脑损伤后应激性溃疡的预防, 应在积极治疗原发颅脑损伤的基础上合理使用质子泵抑制剂、组胺受体拮抗剂和胃黏膜保护剂, 减少胃黏膜病变的发生.

文献来源: 成杰, 蔡丽颖, 唐启群. 中重型颅脑损伤患者继发应激性溃疡机制和防治策略研究进展. 世界华人消化杂志 2024; 32(2): 97-101
URL: https://www.wjgnet.com/1009-3079/full/v32/i2/97.htm
DOI: https://dx.doi.org/10.11569/wcjd.v32.i2.97

0 引言

中重型颅脑损伤是常见的急重性神经外科疾病, 多由高处坠落、车祸和跌倒等意外导致, 病情复杂进展较快, 具有较高病死率严重危害患者生命安全[1]. 应激性溃疡在1969年危重患者尸检时被首次发现[2], 现依据发病严重程度和临床表现将SU分为三类, 发病率分别是15%-50%、1.5%-8.5%和1%-3%[3](表1). 应激性溃疡是中重型颅脑损伤患者的常见并发症之一, 导致原有疾病加重及恶化, 病死率增加. 因此, 通过分析总结中重型颅脑损伤继发应激性溃疡的发病机制和防治策略, 以促进应激性溃疡的规范化治疗.

1 应激性溃疡机制及危险因素

颅内高压是中重型颅脑损伤患者常见的症状, 它损害了脑干和下丘脑的正常生理功能, 干扰自主神经系统功能, 导致其功能发生紊乱, 主要表现为交感神经系统激活同时迷走神经兴奋性增加, 导致儿茶酚胺等神经递质的释放增加和胃酸分泌增多[4,5]. 儿茶酚胺会引发血管收缩, 血容量减少, 从而使得胃黏膜的供血不足, 导致其缺血和缺氧[6-8]. 颅内压增高还会通过下丘脑-垂体-肾上腺皮质轴作用于肾上腺皮质, 促使肾上腺皮质激素大量产生, 在促进胃酸分泌的同时抑制胃黏液、前列腺素分泌以及上皮细胞增生[9]. 以上因素会共同作用于胃黏膜, 使胃黏膜的保护因素减弱, 损害因子增强, 最终引起胃黏膜糜烂、溃疡、出血等严重后果.

颅脑损伤后急性期多有不同程度的胃肠麻痹, 胃肠蠕动减弱甚至消失, 易发生胆汁反流, 造成胃黏膜损伤, 破坏胃黏膜屏障[10]. 颅脑损伤后机体处于高能消耗状态, 蛋白分解加速, 营养供应不足. 胃黏膜中三磷酸腺苷(adenosine triphosphate, ATP)及其他高能磷酸键含量下降, 是胃黏膜损伤的重要原因. 因ATP合成减少, 氧化磷酸化速度减慢而减少了胃黏膜的糖原贮备, 使其对缺血缺氧更为敏感, 而使胃黏膜上皮细胞修复、更新及黏膜分泌功能紊乱, 诱发胃黏膜细胞坏死溃疡形成, 致胃黏膜出血. 黏膜屏障破坏, 使胃酸及胃蛋白酶的刺激增强, 致胃黏膜防御功能减退. 黏膜损伤缺血、细胞肿胀、坏死脱落加快, 使细胞之间的紧密连接和完整性遭到破坏, H+大量逆向渗入. 而胃黏膜表面的上皮细胞因缺氧而坏死, 中和酸的能力下降, 中和反流H+的能力也下降, 而使H+在组织内蓄积, pH值下降导致由于胃黏膜酸化, 极易形成溃疡[11].

应激性溃疡的发病机制比较复杂, 没有办法准确预测其是否会发生, 通过荟萃分析发现, 可能导致应激性溃疡的危险因素包括大脑受伤部位、格拉斯哥评分、机械通气、凝血功能障碍、低血压、肝肾衰竭、肠内营养、糖皮质激素的应用、年龄、糖尿病史、饮酒史、消化道溃疡病史等[12-16]. 由于不同研究的纳入标准和治疗方案不同, 研究结果不能完全相互验证. 目前公认危险因素包括: 正压通气>48 h(包括体外生命支持); 凝血功能异常(血小板计数<50×10^9/L, 国际标准化比率>1.5, 激活部分凝血酶时间>2倍正常值); 既往胃肠溃疡或出血. 在一项包含400例颅脑损伤患者的研究[发生组(n = 50)与未发生组(n = 350)]结果显示: 机械通气时间>48 h患者术后发生应激性溃疡出血的风险是机械通气时间≤48 h患者的23.531倍; 使用抗凝剂或抗血小板聚集药物患者术后发生应激性溃疡出血的风险是未使用抗凝剂或抗血小板聚集药物患者的31.293倍; 消化道溃疡或出血史患者术后发生应激性溃疡出血的风险是无消化道溃疡或出血史患者的36.543倍[17].

此外一些研究表明血液指标的异常也提示了应激

表 1 危重症患者应激性溃疡的分类

类型	临床表现	发病率
应激性溃疡伴隐匿性出血	粪便样本隐血阳性	15%–50%
应激性溃疡伴明显胃肠道出血	呕血, 鼻胃管血吸出, 或黑便	1.5%–8.5%
应激性溃疡伴有严重的胃肠道出血	明显的胃肠出血并且24 h内: 收缩压降低(≥20 mmHg); 直立性低血压或姿势性心动过速(脉率增加≥20次/min); 血红蛋白下降≥2 g/分/升; 需要输血(≥2单位红细胞); 需要血管升压剂或侵入性干预(如内窥镜)	1%–3%

性溃疡发生的可能, 炎症细胞因子是促进应激性溃疡发生的重要因素. 中重型颅脑损伤患者, 往往并发呼吸道和泌尿系统感染, 进而导致脓毒症. 在一项研究中, 重症患者脓毒症的发生率为61.4%, 脓毒症引发炎症细胞因子的大量释放, 加重了脑损伤引起的胃肠运动障碍和胃肠黏膜缺血, 从而促进应激性溃疡的发生[18]. 肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)是一种免疫功能因子, 分泌异常升高可能会损害胃黏膜. Wang等[19,20]研究发现合并应激性溃疡患者的TNF-α含量显著升高. TNF-α的升高导致胃肠道黏膜和内皮细胞的损伤, 从而加重溃疡. 还有研究指出观察组应激性溃疡患者热休克蛋白70(heat shock protein 70, HSP70)和热休克蛋白90(heat shock protein 90, HSP90)是对照组患者的2倍, 血清HSP70、HSP90水平可作为判断重症脑出血病人是否发生应激性溃疡的重要指标[21]. 最新研究显示监测胃液pH值对应激性溃疡有早期预测作用[22]. 临床医生充分了解应激性溃疡发病机制, 及时识别发病危险因素有助于制定个体化精准治疗方案.

2 应激性溃疡的防治

目前还没有关于神经危重症患者应激性溃疡的防治指南. 根据《中国神经外科重症管理专家共识》(2020), 神经外科重症监护中胃肠道溃疡预防管理建议使用质子泵抑制剂(proton pump inhibitor, PPI)(证据级别1级, 推荐A级)、组胺受体拮抗剂(histamine H2 receptor antagonists, H2RA)(证据级别1级, 推荐A级)和胃黏膜保护剂(证据级别1级, 推荐A级)[23]. 东部创伤外科协会实践管理指南委员会也建议, 所有存在相关危险因素的危重症患者都应接受应激性溃疡的预防性治疗[24,25].

通常预防应激性溃疡的预防在中重型颅脑损伤患者入院初就开始实施, 现有的应激性溃疡共识将PPI和H2RA作为高风险人群的标准治疗措施[26-29]. 然而, 一些研究结果对应激性溃疡预防的有效性提出了质疑. 2017年的一项随机对照试验和荟萃分析评估了使用泮托拉唑预防应激性溃疡的有效性, 发现泮托拉唑用于预防应激性溃疡时, 上消化道出血和死亡率没有显著下降[30]. 2018年欧洲一项多中心研究招募了来自丹麦、芬兰、荷兰、挪威、瑞士和英国的33个重症监护病房的3298名患者. 采用盲法、随机对照试验评估了重症监护病房中溃疡高风险患者, 对比了泮托拉唑与安慰剂对应激性溃疡的预防效果, 结果显示, 在接受泮托拉唑预防性治疗的患者中, 2.5%的患者发生了应激性溃疡, 而接受安慰剂的患者发病率为4.2%, 差异不存在统计学意义[31].

应激性溃疡的治疗常规使用PPI或H2RA, 抑制胃酸分泌. 当处于禁食状态时, 胃酸在5-11时分泌率较低, 18时至次凌晨1时分泌较高. PPI的半衰期约为60-90 min, 而其抑制胃酸的作用可持续较长时间[32]. 有研究表明pH>4时, 将有助于血小板聚集和血凝块稳定, 从而降低再出血的风险[33,34]. 考虑到PPI的药代动力学和胃酸分泌的日变化, 每天至少需要给药两次. 但是长期使用PPI与骨折、低镁血症、艰难梭菌感染、急性肾损伤和慢性肾脏疾病的发生有潜在的相关性. 在一项包括18项观察性研究(共244109例骨折病例)的荟萃分析中, Zhou等[35]得出结论, 使用PPI可导致发生骨折的风险增高1.33倍. PPI还可能导致低镁血症, 严重时可导致心律失常、癫痫发作、肌肉无力和低血压, 根据对9项观察性研究(包括109798例患者)的荟萃分析质子泵使用组发生低血镁的风险是非使用组的1.43倍[36]. 除此之外, 使用PPI的患者感染艰难梭菌的风险更高. Kwok等[37]对39项观察性研究进行了荟萃分析, 结果显示, 使用PPI的患者发生艰难梭菌感染的风险是未使用患者的1.74倍, 并且其再次感染艰难梭菌的风险更高. 研究表明, PPI在临床明显消化道出血预防方面比H2RA效果更佳, 此外, 在接受神经危重症治疗的患者中, H2RA可能与抗惊厥药物存在药物相互作用从而加重原发病[28,38,39].

由于研究人员对应激性溃疡预防持有不同观点, 目前尚未形成该疾病预防和治疗的标准指南, 导致临床医生对药物有效性和安全性缺乏充分认识的情况下进行过度防治[40,41]. 虽然预防性用药可以有效降低应激性溃疡的发生率, 但是更应该避免过度预防, 充分认识药物之间的潜在相互作用. 制定合理的防治策略改善神经危重症患者应激性溃疡的治疗现状, 形成标准化防治模式.

3 结论

综上所述, 导致应激性溃疡的危险因素繁多但不明确, 为临床提供了一定的参考价值, 但是很难精准地指导临床应激性溃疡的科学防治, 目前约80%以上的患者预防性使用PPI或者H2RA. 抑酸药的使用可增加医院获得性肺炎、肠道菌群失调、艰难梭菌相关性腹泻等并发症的发生. 由此可见准确评估溃疡风险合理使用抑酸药物非常重要. 我们应该依靠循证医学, 依托于多中心大样本量的研究, 分析应激性溃疡发生风险, 将风险因素赋予不同权重, 制定评估溃疡发生风险临界指标. 依据评估结果精准防治, 科学用药, 形成中重型颅脑损伤患者防治应激性溃疡的规范化治疗.

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科学编辑: 张砚梁 制作编辑: 张砚梁

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton,
CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
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ISSN 1009-3079