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文献综述 REVIEW

炎症性肠病与血栓栓塞性疾病

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Inflammatory bowel disease and thromboembolic events

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Abstract

Thromboembolism (TE) is an extraintestinal manifestation (EIM) of inflammatory bowel disease (IBD). According to previous pathological reports, the incidence of IBD complicated with TE is as high as 41%. However, this EIM is often overlooked. This review summarizes the results of the relevant clinical studies to date, analyzes the potential prothrombotic risk of IBD drug therapy, and discusses the current status on the treatment and prevention of TE, with an aim to provide a comprehensive reference for clinical work.

Key Words: Inflammatory bowel disease; Thromboembolic events; Treatment

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摘要

血栓栓塞是炎症性肠病(inflammatory bowel disease, IBD)的一种肠外表现, 既往病理研究指出IBD合并血栓栓塞的发生率高达41%, 但在日常工作中, 这一肠外表现并未受到足够的重视. 本文总结了目前IBD并发血栓栓塞的临床研究结果, 并对IBD药物治疗的潜在致血栓风险进行了分析, 同时详细阐述了其防治现状, 以期为临床工作提供参考.

关键词: 炎症性肠病; 血栓栓塞性疾病; 治疗

核心提要: 血栓栓塞性疾病(thromboembolic events, TEs)在炎症性肠病(inflammatory bowel disease, IBD)患者中具有较高的发病率和死亡

背景资料

炎症性肠病(inflammatory bowel disease, IBD)的临床表现包括消化系统症状、全身症状及肠外表现. 肠外表现在IBD中有很高的发病率, 同一种肠外表现的复发很常见, 而患一种肠外表现后出现其他种类肠外表现的风险也明显增高, 使IBD的治疗更为复杂. 近年来关于IBD并发血栓栓塞性疾病(thromboembolic events, TEs)的报道越来越多.

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研发前沿

IBD并发TEs受多种因素影响, 尤其与患者炎症状态明显相关, 但其具体机制尚不清楚. 预防性抗凝治疗目前仍颇具争议, 其具体用药方案的安全性及有效性尚待进一步探讨.

率, 本文系统介绍了IBD及其治疗方法与TEs之间的关系, 并详细阐述了其防治现状, 对临床工作中IBD并发TEs的诊断、治疗和预防提供了相关理论依据.

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0 引言

炎症性肠病(inflammatory bowel disease, IBD)包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD), 其复杂多样的肠外表现不仅给患者带来身体上的痛苦, 严重影响其生活质量和工作能力, 更对临床治疗带来了巨大的挑战. IBD肠外表现的发病率约为6%-47%[1], 其中, 血栓栓塞性疾病(thromboembolic events, TEs)(1%-8%)可严重威胁患者生命[2,3]. Grainge等[4]研究指出, 与正常人群相比, IBD患者并发TEs的风险可增加3-4倍, 如疾病处于活动期, 则风险可高达16倍. IBD患者的血栓栓塞主要发生在静脉系统, 以深静脉血栓形成(deep venous thrombosis, DVT)和肺栓塞(pulmonary embolism, PE)最为常见(90.4%), 其他部位如大脑、肾、肝、肠系膜静脉等也可发生栓塞[5]. 近些年来, IBD患者合并TEs逐渐获得国内外学者的重视, 本文旨在针对其研究现状及治疗策略作一综述.

1 IBD与静脉血栓栓塞性疾病

1936年, Bargen等[6]首次报道了UC患者合并静脉血栓栓塞性疾病(venous thromboembolism, VTE)的病例. 随后相关报道逐年增多[7,8]. Talbot等[2]通过对7199例IBD患者进行长达11年的跟踪随访, 发现IBD合并VTE以DVT和PE多见. 有研究指出, 与普通人群相比, IBD患者发生DVT及PE的相对风险为1.96(95%CI: 1.67-2.30)[9], 其中, CD患者DVT的发病率约为31.4/10000人年, PE的发病率约为10.3/10000人年; UC患者DVT的发病率是30.0/10000人年, PE的发病率为19.8/10000人年[10]. Scoville等[11]研究指出, 排除性别与年龄, IBD是DVT发生的独立危险因素. 此外, 活动期的肠道疾病、高同型半胱氨酸血症、脱水、长期卧床、留置导管、吸烟、应用口服避孕药等均为发生DVT的风险因素[12]. 2008年美国胸内科医师学会正式提出IBD是VTE的危险因素[13]. Kappelman等[14]报道, 与老年患者相比, IBD年轻患者并发VTE风险更高, 尤其是在疾病的活动期, 由于血液高凝状态的存在, 肠道微血栓形成增加, 进而引起肠黏膜坏死, 促进溃疡的形成, 进一步加重IBD炎症反应, 如此反复可形成恶性循环.

2 IBD与动脉血栓栓塞性疾病

IBD并发TEs中, 动脉血栓栓塞性疾病(arterial thromboembolic disease, ATED)仅占约18.5%[2]. Osterman等[15]推测, 在IBD患者中普遍存在的肠道炎性环境及血小板功能障碍或许更有利于VTE的发生, 但其具体机制尚不清楚. 目前有关IBD合并ATED的研究众说纷纭. Bernstein等[16]研究指出, IBD患者并发ATED的风险显著增加. 然而, 随后的一项队列研究[17]却指出, 与普通人群相比, IBD患者发生ATED的风险并未增加, 但在亚组分析中, IBD患者并发急性肠系膜缺血的风险明显增加(HR = 11.2, P<0.001), 此外, 40岁以上的女性患者发生心肌梗死的风险增加(HR = 1.6, P = 0.003), 40岁以下的女性IBD患者并发脑卒中的风险可增加约2倍(HR = 2.1, P = 0.04). 近期的一项Meta分析[18]结果显示, IBD患者并发缺血性心脏病(包括心肌梗死)或外周动脉疾病的风险与健康人群相比无明显差异. 这与Lin等[19]关于IBD并发外周动脉疾病的研究结果相悖. 未来仍需大规模临床研究以明确IBD与ATED之间的关系.

3 IBD的药物治疗与TEs

3.1 氨基水杨酸类制剂 柳氮磺吡啶(sulfasalazine, SASP)是最早用于IBD治疗的氨基水杨酸类制剂. SASP可抑制二氢叶酸还原酶的活性, 导致叶酸缺乏, 从而形成高同型半胱氨酸血症[20]. 既往大量研究[12,21]显示高同型半胱氨酸血症是心脑血管疾病及DVT发生的危险因素. Wei等[22]曾报道强直性脊柱炎患者在应用SASP治疗后, 血浆同型半胱氨酸水平显著增加, 但SASP用于IBD人群能否得出相同结论有待商榷.

近些年来, 新型5-氨基水杨酸类制剂(5-aminosalicylic acid, 5-ASA)获得广泛应用. 5-ASA可影响IBD患者的血小板功能, 但其作用机制莫衷一是. 体外研究结果表明, 5-ASA可

直接抑制血小板激活[23]; 在体试验则指出, IBD患者应用5-ASA治疗后, 其体内血小板表面的P选择素表达明显减少[23], 同时, 促进血小板聚集的趋化因子水平明显降低[24]. 然而, 这些结论并未在相关临床研究中得到进一步证实[25].

3.2 糖皮质激素 糖皮质激素(glucosteroid, GCS)主要用于中、重度IBD患者及对5-ASA治疗无效的轻型患者. GCS可直接或间接损伤血管内皮细胞, 启动外源性凝血途径; 此外, 在GCS的作用下, 血小板释放大量血小板源性微粒, 同时得以活化, 激活内源性凝血途径. 在两者的共同作用下, 血液处于高凝状态. El Accaoui等[26]研究发现, 应用地塞米松可增加VTE的发生风险. 随后, Wallaert等[27]指出, GCS是IBD患者术后静脉血栓形成的潜在危险因素. 近期, 一项回顾性单中心队列研究[28]结果表明, 约36%并发TEs的IBD患者曾在发病前应用GCS治疗. 此外, 目前已有研究[29]证实GCS可增加缺血性心脏病的发病风险.

3.3 免疫抑制剂 硫唑嘌呤(azathioprine, AZA)及其代谢产物6-巯基嘌呤(6-mercaptopurine, 6-MP)是IBD治疗中最为常用的免疫抑制剂. 既往研究[20,30-32]显示, AZA及6-MP可通过抑制二磷酸腺苷减少血小板聚集, 同时降低IBD患者体内白细胞聚集体水平, 从而抑制血栓形成, 降低IBD患者并发TEs的风险.

甲氨蝶呤是叶酸拮抗剂, 可使血浆同型半胱氨酸水平升高, 进而增加IBD患者血栓栓塞事件的发生风险, 但这一点尚未在临床研究中得到进一步证实[33].

环孢素A(cyclosporin A, CsA)可促进血小板聚集, 激活血管内皮细胞, 并损伤纤溶系统, 从而使患者体内凝血活性升高[31,34,35]. Al-Shekhlee等[36]发现服用CsA的IBD患者血栓栓塞事件明显增多.

他克莫司常用于难治性UC和CD合并肠瘘的治疗. Wang等[37]研究指出, 细胞色素P450酶(cytochrome P450, CYP450)3A4和CYP3A5的遗传多态性是影响他克莫司不良反应发生率的重要因素. Asrani等[38]在一项多中心研究中发现, 他克莫司的应用会增加血栓发生率. 目前国内相关研究较少, 仅王静等[39]曾在2016年报道他克莫司致血栓性静脉炎1例.

沙利度胺不良反应较多, 临床应用较少. 既往有研究[40]指出, 沙利度胺单独应用时静脉血栓发生率约为1%-5%, 而与地塞米松联合应用时, PE和DVT的发生率可增加至30%. 目前尚缺乏沙利度胺致血栓栓塞机制方面的系统研究, 或与内皮细胞活化和纤溶系统异常有关[41].

3.4 生物制剂 目前, IBD的治疗已进入生物制剂的时代. 既往研究指出, 约4.5%应用肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)拮抗剂治疗的患者出现TEs[42], 其中以VTE多见[43]. Kim等[44]研究指出, 与应用传统药物治疗的患者相比, 应用生物制剂治疗的患者短期内发生VTE风险增加(HR = 1.83, 95%CI: 0.91-3.66).

英夫利昔单抗(infliximab, IFX)是一种人-鼠嵌合型TNF-α单克隆抗体, 目前应用相对广泛. IFX可通过下调肠黏膜微循环中的CD40/CD40L通路进而抑制血小板活化, 同时可明显降低IBD患者体内循环颗粒的数量[45,46]. 有报道指出, IFX可使IBD患者的凝血参数趋于正常[47,48]. 但是, 在IBD患者应用IFX治疗的过程中, 也有合并肾静脉血栓形成的案例报道[49], 这可能与其诱导产生的抗磷脂抗体相关[50,51].

此外, 阿达木单抗(adalimumab, ADA)、戈利木单抗、维多珠单抗及伊那西普等逐渐登上IBD治疗的舞台, 但这些药物多数尚处于临床前期研究阶段, 相关数据较少. 近年来, 一项针对ADA治疗患者的队列研究[52]结果表明, 体内产生ADA抗体的患者更易发生TEs(HR = 7.6, 95%CI: 1.3-45.1). 目前已有病例报道指出伊那西普或与VTE发生相关[53,54]. 未来仍需大规模临床研究以明确生物制剂的应用与TEs之间的关系.

4 IBD并发TEs的治疗

4.1 低分子肝素 2014年, 加拿大IBD与静脉血栓防治共识意见中正式提出: IBD住院患者如果没有合并活动性出血或非大量出血推荐常规予以抗凝治疗[55]. 然而, 目前针对预防性抗凝治疗仍存在较大争议. 既往研究[56]发现, 低分子肝素(low molecular weight heparin, LMWH)具有修复肠道黏膜的作用, 应用口服型LMWH治疗轻、中度IBD患者, 临床缓解率可高达70%. 近来Chande等[57]的研究显示, 轻、中度UC患者口服LMWH肠溶缓释片的疗效优于安慰剂组, 但皮下注射小剂量LMWH或普通肝素(unfractionated heparin, UH)对UC

相关报道
Celasco等的研究显示, 给予轻中度溃疡性结肠炎患者口服低分子肝素新型制剂, 其临床活动指数、内镜指数及组织学评分均优于安慰剂组, 证实了其临床有效性.

创新盘点

本文结合国外防治共识及相关临床数据, 对预防性抗凝治疗的现行方案、新药物、新剂型及新方案进行了详细介绍.

患者病情缓解无意义. 另有研究[58]指出, 应用LMWH皮下注射可改善轻、中度活动性UC患者的部分炎症和凝血指标, 但对临床症状和内镜下表现无作用. 因此, 对于不存在高凝状态的IBD患者, 通常不建议应用UH或LMWH预防血栓形成; 对于处于高凝状态的患者, 则可考虑给予适量LMWH治疗, 但同时应警惕出血等不良反应[59]. 此外, 抗凝药物的应用需在遵守国际准则的同时根据患者病情作出相应调整. 对急性肾静脉栓塞和PE的患者, 应持续使用LMWH至少3 mo, 或将Xa因子抑制剂用于初始治疗, 随后换用维生素K拮抗剂[60].

4.2 其他 阿司匹林具有抗血小板聚集的作用. 既往曾有学者尝试在IBD缓解期加用阿司匹林以降低其并发TEs的风险, 取得了良好的效果[61]. 但是, 阿司匹林对肠黏膜的损伤作用不容忽视[62], 既往亦有报道指出应用阿司匹林可导致UC复发[63]. Mehta等[64]研究发现, 高剂量与低剂量阿司匹林在预防TEs发生方面, 疗效无明显差异, 但应用低剂量(81-100 mg)阿司匹林可有效降低出血风险, 这为阿司匹林应用于IBD的维持治疗提供了新的思路.

目前已有华法林用于治疗IBD并发TEs的相关报道[65], 但尚缺乏其有效性及安全性的大规模研究. 由于华法林治疗窗窄, 个体差异大, 应用过程中需要定期监测国际标准化比值, 极大地限制了其临床应用.

达比加群酯是一种新型口服抗凝药物, 几乎不受食物影响, 与药物相互作用少, 使用过程中无需频繁监测凝血功能, 临床应用更为方便, 但其价格高昂, 长期应用将给患者带来较重的经济负担, 可间接影响患者依从性. 其他新兴药物如利伐沙班等, 近些年来逐渐受到重视, 为IBD并发TEs的防治带来新的曙光.

5 总结

随着大规模流行病学研究的开展, TEs作为IBD的肠外表现受到越来越多的关注. IBD并发TEs死亡率高, 预后差, 其发生机制尚不清楚, 可能与血管内皮损伤、血液黏稠度、血小板计数及活化异常、凝血及纤溶系统异常等有关, 此外, 几乎所有用于治疗IBD的药物均可影响患者的凝血功能, 或可增加TEs的发病风险. 目前, 关于IBD并发TEs的预防性抗凝治疗仍存在一定争议. 近些年来, 新药物、新剂型和新方案层出不穷, 未来仍需大规模随机对照试验以探讨其安全性及有效性.

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应用要点

本文总结了目前IBD并发血栓栓塞的临床研究结果, 并对IBD药物治疗的潜在致血栓风险进行了分析, 同时详细阐述了其防治现状, 对临床工作具有较好的指导意义.

同行评价

本文系统介绍了IBD及其治疗方法与TEs之间的关系, 并详细阐述了其防治现状, 文章设计合理, 证据应用准确, 具有一定新颖性和创新性.

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• 消息 •

《世界华人消化杂志》性质、刊登内容及目标

本刊讯 《世界华人消化杂志》[国际标准刊号ISSN 1009-3079 (print), ISSN 2219-2859 (online), DOI: 10.11569, *Shijie Huaren Xiaohua Zazhi*/*World Chinese Journal of Digestology*], 是一本由来自国内31个省、市、自治区、特别行政区和美国的1040位胃肠病学和肝病学专家支持的开放存取的同行评议的旬刊杂志, 旨在推广国内各地的胃肠病学和肝病学领域临床实践和基础研究相结合的最具有临床意义的原创性及各类评论性的文章, 使其成为一种公众资源, 同时科学家、医生、患者和学生可以通过这样一个不受限制的平台来免费获取全文, 了解其领域的所有的关键的进展, 更重要的是这些进展会为本领域的医务工作者和研究者服务, 为他们的患者及基础研究提供进一步的帮助.

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