世界华人消化杂志®
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世界华人消化杂志 2012年4月28日; 20(12): 1030-1035
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

肝小静脉闭塞病的临床现状及研究进展

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■背景资料
肝小静脉闭塞病(hepatic veno-occlusive disease, HVOD)是造血干细胞移植的主要并发症之一. 目前该病的预防和治疗缺乏成熟方案, 各种药物都需要进一步试验证实其疗效, 其中去纤苷疗效最确切, 其研究最为深入, 即将进入Ⅲ期临床实验.

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收稿日期: 2012-02-10 修回日期: 2012-03-14
接受日期: 2012-03-28 在线出版日期: 2012-04-28

Clinical research of hepatic veno-occlusive disease: current status and future prospects

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Received: 2012-02-10 Revised: 2012-03-14
Accepted: 2012-03-28 Published online: 2012-04-28

Abstract
Hepatic veno-occlusive disease (HVOD) is one of the main complications of hematopoietic stem cell transplantation (HSCT). Its pathogenesis is mainly associated with a local hypercoagulable state, and the main pathological changes are occlusion of terminal hepatic venules and necrosis of liver cells. The diagnosis of HVOD depends on a liver biopsy. Identifying and avoiding the risk factors are main measures to reduce the incidence and mortality of HVOD, since drug prophylaxis lacks exact effect and has significant adverse reactions. Defibrotide is the most effective therapy for HVOD, while the efficacy of other drugs still needs to be verified. In this paper, we will review the current status and future prospects of clinical research of HVOD.

Key Words: Hepatic veno-occlusive disease; Prophylaxis; Therapy; Defibrotide

Peng Q, He DZ, Li JS. Clinical research of hepatic veno-occlusive disease: current status and future prospects. Shijie Huaren Xiaohua Zazhi 2012; 20(12): 1030-1035

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摘要
肝小静脉闭塞病(hepatic veno-occlusive disease, HVOD)是造血干细胞移植(hematopoietic stem cell transplantation, HSCT)的主要并发症之一. 其发病机制主要是局部高凝状态, 主要病理改变是终末肝小静脉的闭塞及肝细胞的坏死. HVOD的确诊依靠肝组织活检. 明确并避免危险因素是降低HVOD的发病率及死亡率的主要措施, 药物预防效果尚不确切并且多有不良反应. HVOD的治疗以去纤苷的效果最为肯定, 其他药物的疗效仍需验证. 本文就HVOD的临床现状及研究进展作一综述.

关键词: 肝小静脉闭塞性疾病; 预防; 治疗; 去纤苷

彭俏, 贺德志, 李建生. 肝小静脉闭塞病的临床现状及研究进展. 世界华人消化杂志 2012; 20(12): 1030-1035
http://www.wjgnet.com/1009-3079/20/1030.asp

0 引言
肝小静脉闭塞病(hepatic veno-occlusive disease, HVOD), 也称为肝窦阻塞综合征(sinusoidal obstruction syndrome, SOS). 早在1953年Hill等[1]便对该病进行了详细描述. HVOD以疼痛性肝肿大、体液潴留、黄疸为主要症状. HVOD是造血干细胞移植(hematopoietic stem cell transplantation, HSCT)的主要并发症之一, 不同研究报告其发生率在5%-70%[2]. 大量摄入含有吡咯烷生物碱(pyrrolizidine alkaloids, PA)的草药也是主要病因. 食用被PA污染的面粉、蜂蜜、动物奶等可造成HVOD的流行[3]. 其他病因有放化疗、器官移植、口服避孕药、摄入酒精等[2,4,5]. 针对HVOD的研究已有很长时间, 我们对其发病机制及组织病理已有深入了解, 在诊断上也有成熟方法. 由于HVOD的早期诊断困难并且重症患者死亡率高, 其预防及治疗十分重要, 但目前预防及治疗方法均不成熟并且有很大的研究空间, 这篇综述将总结HVOD的临床现状和

研究进展, 特别是预防和治疗领域的成果和研究方向.

1 HVOD的发病机制及组织病理学

HVOD发生时, 肝小静脉内皮及肝窦内皮受到损伤, 促使TNFα、IL-1β、von Willebrand因子(von Willebrand factor, vWF)等细胞因子释放, 激活外源性凝血途径, 促进血小板凝集, 同时抗凝血酶复合物作用减弱, 造成局部高凝状态并形成血栓, 导致肝窦和终末肝小静脉闭塞[6-11]. 血NO水平下降造成血管收缩, 加重血供障碍[12]. 肝腺泡Ⅲ带肝细胞由于缺血而坏死. TNFβ水平升高促使成纤维细胞向受损部位迁移增殖并合成大量胶原蛋白, 导致肝脏纤维化[13]. 免疫因素也可能参与HVOD的发病机制.

HVOD的早期组织病理学表现为肝小静脉的损伤, 包括内皮下水肿、红细胞渗出和纤维蛋白、巨噬细胞、vWF在血管壁的沉积[6,14,15], 继而进展至终末肝小静脉和肝窦的向心性狭窄、肝窦充血及不同程度的肝小叶中央凝固性坏死. 晚期由于胶原蛋白的沉积, 内皮下及动脉外膜纤维化, 最终进展为肝硬化[16-18].

2 HVOD的诊断

HVOD的临床诊断遵照Seattle标准[19,20]和Baltimore标准[21]. Seattle标准指HSCT后30 d内出现黄疸、疼痛性肝肿大、体液潴留3项症状中至少2项. Baltimore标准指HSCT后21 d内出现高胆红素血症(血清总胆红素>34.2 μmol/L)合并下列症状中至少2项: 疼痛性肝肿大, 体质量增加>5%, 腹水. 根据病程及预后, HVOD可分为轻、中、重度, 轻度HVOD可自愈, 中度HVOD经治疗后可完全缓解, 重度HVOD长期无缓解(>100 d)且死亡率达98%[19].

HVOD的超声表现有腹水, 肝肿大, 胆囊壁增厚, 肝脏血流信号衰减, 肝静脉显示不清, 门静脉血流减慢甚至离肝血流, 肝动脉阻力指数可能升高[2,6,22-24]. Lassau等[25]提出的多普勒超声定量评分有助于早期诊断HVOD并预测其严重程度. CT表现为肝动脉增粗迂曲, 肝实质呈“地图状”、斑片状强化, 肝静脉显示不清, 下腔静脉肝段受压, 下腔静脉、门静脉周围“晕环征”或“双轨征”, 门静脉血栓形成[26-28].

诊断HVOD的金标准是肝组织活检. 由于HVOD多伴有凝血功能异常, 经皮肝穿可能引起大出血等严重后果, 故应用受限. 经颈静脉肝组织活检能减小出血风险并获取足量的组织样本[6]. 经颈静脉测量肝静脉压力梯度(hepatic venous pressure gradient, HVPG)>10 mmHg对HVOD的诊断特异性达90%以上[29]. 一些血液生化指标如蛋白质C、抗凝血酶Ⅲ(antithrombin Ⅲ, ATⅢ)值的降低和纤溶酶原激活物抑制物-1(plasminogen activator inhibitor type 1, PAI-1)、Ⅲ型前胶原肽值的升高有助于早期诊断HVOD[6,30,31]. 另外血清透明质酸、vWF裂解蛋白酶及CA125也能作为HVOD的早期标志物[19].

3 HVOD的预防

3.1 明确并避免HVOD的危险因素 预防HVOD的主要措施是明确并避免危险因素. 已知HVOD的危险因素有: (1)基础肝病, 如乙肝、丙肝、肝纤维化、肝硬化; (2)既往有HVOD病史或HSCT预处理史; (3)高剂量的全身放疗, 特别是肝区放疗; (4)近期使用过吉妥珠单抗奥唑米星; (5)预处理方案包含环磷酰胺, 口服白消安或白消安的剂量过大; (6)预处理过程中应用两性霉素B、万古霉素、阿昔洛韦抗感染治疗; (7)HSCT患者使用环孢素A、甲氨蝶呤预防移植物抗宿主病; (8)携带血色病C282Y等位基因等[6,19,22]. 有研究指出异基因造血干细胞移植者患HVOD的风险较自体造血干细胞移植(autologous HSCT, auto-HSCT)者大[32]. 对于具有以上危险因素的患者, 采用低强度预处理方案, 静脉应用白消安并个体化用药, 预处理中用氟达拉滨替代环磷酰胺和低剂量全身放疗可降低HVOD的发病率[33-37]. 女性HSCT患者使用炔诺酮增加患HVOD的风险, 应避免应用此类药物[38].

3.2 药物预防 肝素、前列腺素E1、熊去氧胆酸(ursodeoxycholic acid, UDCA)、己酮可可碱在一些随机对照试验中被证实有预防HVOD的效果[22]. 肝素降低高危人群HVOD患病率的效果仍不确切, 并可能引起致命性出血[6,22]. 前列腺素E1有舒张血管、抗凝和溶栓作用, 但使用过程中可能出现低血压、肢端疼痛、水肿、皮肤水疱等严重药物不良反应[39]. UDCA在一些随机对照试验中预防HVOD效果明显并且药物不良反应小. Essell等[40]的试验中, 试验组和对照组HVOD的发病率分别为15%和40%, Ohashi等[41]的试验中则分别为3.0%和18.5%. 然而另2项试验却未证实UDCA有明显的预防作用[42,43]. 己酮可可碱是一种甲基黄嘌呤类似物, 可抑制TNFα相关基因转录, 其在预防HVOD方面应用较少,

■研发前沿
HVOD的早期诊断方法如多普勒超声定量评分及血清标志物的研究, 治疗药物如去纤苷、甲泼尼龙的疗效评价, 都逐渐受到关注.

■创新盘点
本文总结了HVOD诊断、预防、治疗的现状, 并特别关注了预防及治疗方面存在的问题及发展方向.

效果尚待证实[6]. 一项历史对照研究显示对于血清铁蛋白显著升高(>1 000 ng/L)并接受大剂量化疗及auto-HSCT的患者, 应用铁螯合剂可降低HVOD的发病率, 但该种药物可能导致肾功能不全[44]. Chalandon等[45]的历史对照研究显示去纤苷联合肝素可有效预防HVOD(试验组发病率0, 对照组发病率19%), 并且无药物不良反应. 国内刘嘉等[46]运用中西医结合方法, 采用复方丹参注射液联合前列腺素E1、低分子肝素钙及右旋糖酐预防HSCT后HVOD, 效果良好(发病率0.19%), 并且未出现凝血功能障碍等药物不良反应.

4 HVOD的治疗

4.1 对症支持治疗 确诊HVOD或出现疑似症状时, 避免继续应用肝毒性药物并进行保肝治疗. HVOD的致死原因主要是多器官功能衰竭(multiple organ failure, MOF)[22], 所以对症支持治疗是基本措施. 对症支持治疗的主要目的是维持水电解质平衡、解除体液潴留并维持有效循环血量和肾灌注. 限水限钠及利尿治疗能减轻体液潴留, 严重潴留者可行浆膜腔穿刺抽液. 白蛋白和血浆因最终积聚在间质从而加重体液潴留, 二者的应用仍有争议. 肾功能衰竭的患者行血液透析. 出现呼吸衰竭时给予吸氧或机械通气. 重症患者还需纠正凝血功能异常及抗感染治疗[2,6,19,22].

4.2 重组组织型纤溶酶原激活剂 由于HVOD患者局部血液处于高凝状态, 故促纤维蛋白溶解和抗凝是有效的治疗方法. 已有病例分析研究了单独应用重组组织型纤溶酶原激活剂(recombinant tissue plasminogen activator, rt-PA)或与肝素联合应用的治疗方法. 一项包括42名HVOD患者的病例分析显示联合应用rt-PA和肝素治疗的应答率为29%, 但治疗过程中10名患者发生严重出血, 并且重度HVOD合并MOF患者的应答率低下[47]. 在另一项包括17名HVOD患者的病例分析中rt-PA治疗的应答率为29%, 百日生存率33%, 无应答的患者大部分有既往肝损害病史并且百日生存率为0[48], 由于其中12名患者同时应用了肝素, 该试验无法确证rt-PA的疗效. 目前缺乏rt-PA治疗HVOD的大样本随机对照试验. 由于rt-PA治疗重度HVOD效果不佳并且能诱发致命的脑出血或肺出血[49], 建议早期干预并小剂量应用.

4.3 去纤苷 去纤苷是一种寡核苷酸, 能调节血小板活性, 抑制凝血酶释放及其活性, 下调PAI-1水平, 有局部抗血栓形成及抗炎作用, 并促进纤维蛋白溶解, 选择性作用于小血管[50]. 去纤苷治疗HVOD效果肯定且药物不良反应小, 是近年来研究的热点. 在一项多机构临床研究中, 采用去纤苷治疗88名重度HVOD患者(静脉用药, 5-60 mg/(kg·d), 中位应用时间为15 d), 完全缓解(complete response, CR)率为36%, 百日生存率为35%, 无出血等明显不良反应. 年龄较小、auto-HSCT、门静脉血流异常、治疗过程中肌酐和PAI-1水平降低者生存率较高, 但预处理中应用白消安及出现脑病者预后较差[51]. Corbacioglu等[52]对45例应用去纤苷治疗儿童HVOD的病例进行回顾分析, 总CR率为76%, 百日生存率为64%, 重度HVOD组的CR率及长期生存率分别为50%和36%, 去纤苷剂量可能与应答率呈正相关(应答组平均剂量45 mg/(kg·d), 无应答组平均剂量27 mg/(kg·d)), 并且早期干预对CR有显著意义. 近年一项多中心Ⅱ期随机量效试验肯定了不同剂量(25 mg/(kg·d), 40 mg/(kg·d))的去纤苷对重度HVOD的疗效, 儿童患者、早期治疗患者的CR率和生存率较高, 大剂量组和小剂量组的总体CR率及生存率无显著性差异, 药物不良反应发生率低且两组之间无显著性差异. 研究小组拟选择25 mg/(kg·d)的剂量进行Ⅲ期临床试验[50]. 在另一项临床对照试验中, 所有患HVOD的受试者均表现出ATⅢ活性的降低, 试验组应用ATⅢ联合去纤苷治疗后CR率达100%, 百日存活率为93%, 对照组未进行治疗, 百日存活率为46%, 该试验未验证去纤苷和ATⅢ是否有协同作用[53].

4.4 甲泼尼龙 Khoury等[54]用大剂量甲泼尼龙冲击治疗20名HVOD患者(500 mg/m^2, iv, q12h, 共6次), 应答率60%. 在Al Beihany等[55]的临床研究中, 48名HVOD患者应用甲泼尼龙治疗后(0.5 mg/kg, iv, q12h, 共14次, 骤停), 30名患者胆红素下降超过50%. 目前缺乏甲泼尼龙治疗HVOD的大样本随机对照试验, 其治疗HVOD的效果需进一步研究证实.

4.5 经颈静脉肝内门体分流术 经颈静脉肝内门体分流术(transjugular intrahepatic portosystemic shunt, TIPS)用于治疗HVOD引起的门脉高压. Azoulay等[56]的临床研究中, 10名重度HVOD患者接受TIPS后, HVPG均下降, 其中5人病情无好转, 因MOF于10 d内死亡, 另5人ALT、肌酐等指标有明显改善, 其中4人于TIPS后11-54 d死亡, 1人持续生存超过6 mo, 因此单纯解决门脉高压不足以提高重度HVOD患者的生存率, 后续治疗

仍然十分关键. 由于TIPS不能改善HVOD患者的预后, 故最近指南不建议TIPS治疗HVOD[22].

4.6 肝移植 当内科治疗不能逆转病情, 最终出现肝衰竭的HVOD患者可以考虑肝移植, 目前成功的肝移植仅见于个案[57-59]. 筛选合适的患者可提高肝移植的成功率. 恶性肿瘤及MOF是肝移植的禁忌证[19,22]. 如果HVOD本身是由肝移植引起的, 只要不合并其他脏器的损害, 可以行第二次肝移植[19].

5 结论

HVOD的临床难点在于预防及治疗. 明确并避免HVOD的危险因素对于预防十分重要. 预防性药物选择众多但有效性均没有被完全证实, 并且多数药物有程度不等的不良反应. HVOD的治疗以药物为主, 去纤苷疗效确切并且无明显药物不良反应. TIPS及肝移植对于HVOD的治疗应用范围十分有限并且效果欠佳. 今后在药物预防及治疗方面的深入研究将会进一步降低高危人群的HVOD发病率及死亡率.

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■名词解释

去纤苷: 抗凝血药物, 是一种寡核苷酸, 市售产品由猪、牛、羊等哺乳动物肺中提取而得. 具有明显的纤溶作用, 通常用于预防深静脉血栓形成及血栓性静脉炎的治疗.

■同行评价
本文阐述了HVOD的概况及一些进展, 条理清晰, 具有一定新意, 并具有较好的临床借鉴意义.

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编辑 张姗姗 电编 闫晋利

ISSN 1009-3079 (print) ISSN 2219-2859 (online) CN 14-1260/R 2012年版权归世界华人消化杂志

• 消息 •

《世界华人消化杂志》再次入选《中文核心期刊要目总览》(2011年版)

本刊讯 依据文献计量学的原理和方法, 经研究人员对相关文献的检索、计算和分析, 以及学科专家评审, 《世界华人消化杂志》再次入选《中文核心期刊要目总览》2011年版(即第六版)核心期刊.

对于核心期刊的评价仍采用定量评价和定性评审相结合的方法. 定量评价指标体系采用了被索量、被摘量、被引量、他引量、被摘率、影响因子、被国内外重要检索工具收录、基金论文比、Web下载量等9个评价指标, 选作评价指标统计源的数据库及文摘刊物达到60余种, 统计到的文献数量共计221177余万篇次, 涉及期刊14400余种. 参加核心期刊评审的学科专家达8200多位. 经过定量筛选和专家定性评审, 从我国正在出版的中文期刊中评选出1982种核心期刊.

《世界华人消化杂志》在编委、作者和读者的支持下, 期刊学术水平稳步提升, 编校质量稳定, 再次被北京大学图书馆《中文核心期刊要目总览》(2011年版)收录. 在此, 向关心、支持《世界华人消化杂志》的编委、作者和读者, 表示衷心的感谢! (编辑部主任: 李军亮 2012-03-08).