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新型口服抗凝药在肝硬化合并门静脉血栓的治疗进展

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摘　要

门静脉血栓(PVT)是肝硬化患者的常见并发症，可合并腹水、凝血功能异常、静脉曲张出血等。目前抗凝治疗作为一线治疗。与传统抗凝药相比，新型口服抗凝药具有起效快、不需要常规监测、食物药物相互作用较少，越来越受到关注。但是新型口服抗凝药用于治疗肝硬化合并PVT的相关研究较少。本文就新型口服抗凝药用于治疗肝硬化合并PVT患者的现有文献进行综述。

关键词

肝硬化，门静脉血栓，抗凝治疗，新型口服抗凝药

Advance of New Oral Anticoagulants in the Treatment of Portal Vein Thrombosis in Cirrhosis

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Abstract

Portal vein thrombosis (PVT) is a common complication in cirrhotic patients, usually companying with ascites, coagulation abnormalities, and variceal bleeding. Anticoagulation is currently used as first-line therapy. The use of the new oral anticoagulants (NOACs) for the treatment of PVT is raising concerns as they have a rapid onset of action, no requirement for routine coagulation mon-

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itoring, and a smaller number of food-drug interactions compared to traditional anticoagulants. However, few studies have discussed the use of NOACs in the treatment of cirrhosis with PVT. The purpose of this review is to evaluate the existing literature on the advance of NOACs in the treatment of cirrhosis patients with PVT.

Keywords

Cirrhosis, Portal Vein Thrombosis, Anticoagulation Therapy, New Oral Anticoagulants

1. 引言

肝硬化是慢性肝病的最后阶段，以肝实质的纤维化和再生结节为特征。广泛的肝纤维化会导致门脉压力升高和门体分流，并伴有外周血管扩张和高动力循环。这些都会使得肝硬化患者门静脉血栓(portal vein thrombosis, PVT)的风险增加[1]。PVT 是指在门静脉主干或肝内门静脉分支内形成血栓，可分为闭塞性/完全性和部分性/不完全性，最终会延伸至肠系膜上静脉，从而危及患者生命[2] [3] [4]。肝硬化是 PVT 的独立危险因素[5]，并且 PVT 的发生率与肝硬化的严重程度成正比，在代偿期肝硬化患者中低于 1%，但在晚期失代偿期肝硬化患者中，PVT 的发病率高达 7.4%~16% [6]。另外，大约三分之一的肝硬化患者会发生门静脉血栓自发再通，但接受抗凝治疗能够提高肝硬化后 PVT 的再通率，使患者获益更多[7]。目前较常使用的抗凝药物包括传统抗凝药(肝素类、维生素 K 拮抗剂)和新型口服抗凝药(new oral anticoagulants, NOACs)。对于肝硬化合并门静脉血栓的患者，临床指南和共识声明建议使用低分子肝素(low-molecular-weight heparin, LMWH)或维生素 K 拮抗剂(vitamin K antagonists, VKA) [8] [9]。与这些传统抗凝药相比，NOACs 因具有起效快、药效稳定、不需要常规监测，在临床上的使用越来越广泛[10]。此外，最近的报道表明，在预防和治疗静脉血栓方面，NOACs 的疗效和安全性与传统抗凝药相当，甚至更好[11] [12] [13]。但是，关于 NOACs 的高质量研究证据不充分，各相关指南和共识仅将其列入可选药物之一，在最新的 Baveno Ⅶ共识中其证据级别为 C1 或 C2 [9] [14] [15]。本文结合相关现况研究，对 NOACs 在肝硬化合并 PVT 的治疗进展作一综述。

2. 肝硬化合并 PVT 的形成机制

Virchow 三联征(静脉血流淤滞、高凝状态和血管内皮功能损伤)是肝硬化患者发生 PVT 的主要因素。首先，肝硬化患者常常出现高凝状态，表现为蛋白 C、蛋白 S、抗凝血酶 III、血浆蛋白原减少，以及血浆蛋白原激活剂抑制剂增加[3]。VIII 因子水平的增加也与 PVT 发生的风险有关。据报道，肝硬化患者血浆中 VIII 因子的水平超过 129 IU/dL，PVT 发生的风险增加 6 倍[16]。相比之下，门静脉血流淤滞对肝硬化患者发生 PVT 的影响更大。MCCONNELL 等[17]研究报道，当门静脉血流速度降至 15 cm/s 以下时，PVT 的风险增加 6~24 倍。对门静脉内皮造成直接或间接损伤的因素，如腹腔创伤或手术、内镜下静脉曲张治疗、炎症或内毒素等，都可促使肝硬化患者发生 PVT [18]。

3. 肝硬化合并 PVT 的疗程

抗凝治疗通常被推荐为一线治疗，不仅可提高 PVT 再通率，降低 PVT 进一步进展，延缓肝功能进

Observational 一步加重，还能提高生存率，其益处已经在肝硬化合并 PVT 的患者中得到证实[19]。但是一部分肝硬化合并 PVT 的患者常常没有明显症状或者被偶然性诊断，早期诊断和早期开始抗凝对于提高门静脉再通、预防并发症、改善患者预后至关重要。一旦确诊肝硬化病人合并 PVT 或者有潜在血栓形成因素，就应尽早开始抗凝治疗[20] [21]。

各项指南对肝硬化合并 PVT 的抗凝推荐时间有所不同。美国肝病研究协会指南建议，所有急性 PVT 患者至少抗凝 3 个月，合并肠系膜静脉血栓的患者或有永久性血栓危险因素的患者应长期抗凝[22]。欧洲肝病研究学会(EASL)和美国胃肠病学会(ACG)指南建议肝硬化 PVT 患者至少抗凝 6 个月，对于血栓延伸至肠系膜静脉的患者、有肠道缺血病史的患者或肝移植候选人，考虑终身抗凝[8] [23]。2020 年上海肝硬化合并门静脉血栓形成的治疗共识中提到，在一些肝硬化 PVT 的患者中，六个月的抗凝治疗可能不足以实现门静脉再通；对于此类患者，抗凝时间应延长至 12 个月[24]。对于不同肝硬化严重程度、门静脉血栓分布范围，有无合并肠系膜静脉血栓的患者，抗凝持续时间应该个体化、综合化考虑。

4. NOACs 的疗效与安全

NOACs 包括 Xa 因子直接抑制剂(利伐沙班、阿哌沙班和依度沙班)和Ⅱa 因子抑制剂(达比加群酯)。相比于传统抗凝药，NOACs 具有以下优点[25]：1) 不需要常规监测抗凝强度(华法林需要定期监测 INR)；2) 口服制剂，一般治疗人群不需要调整剂量，依从性好；3) 口服后吸收快，药代动力学和药效学稳定，起效快(如：利伐沙班的起效时间为 30 分钟，相比华法林需要 36~72 小时)；4) 半衰期较短，停药后抗凝作用消失较快；5) 很少受到食物、药物的影响。在过去的十年内，NOACs 在获得批准后被越来越多地用于预防非瓣膜性房颤的患者发生中风和治疗血栓栓塞性疾病，如静脉血栓栓塞和肺栓塞，但其在肝硬化患者中使用的证据非常有限[26] [27]。

NOACs 的抗凝效果逐渐得到肯定。首先，在关于静脉血栓栓塞治疗和二级预防的 III 期临床试验中，NOACs 相比于传统抗凝药，不仅表现出相当或更好的疗效，而且体现出相同或较低的出血风险[28] [29] [30]。在肝硬化合并 PVT 中，目前相关研究提示 NOACs 的有效性不劣于或优于传统抗凝药，且并未增加出血、死亡的风险[31] [32] [33] [34]。Ng 等[31]纳入 10 篇文献，经过 Meta 分析发现，NOACs 治疗组中 79.5%的患者达到了完全或部分血栓再通，出血率为 9.8%。NOACs 在血栓完全再通率上，明显优于 LMWH 或 VKA 或未抗凝的患者，但在部分再通率上则未优于其他治疗，而出血和死亡风险与传统抗凝药相当。

与非肝硬化 PVT 的抗凝治疗不同，肝硬化 PVT 患者常常合并腹水、凝血功能异常、静脉曲张出血等。因此，抗凝用药会受到患者基础疾病、凝血功能等多因素的影响。对于轻度肝功能不全(Child-Pugh A)患者，NOACs 均可使用，没有明显的出血风险[35]。对于中度肝功能不全(Child-Pugh B)患者，应谨慎使用达比加群、阿哌沙班和依度沙班，而利伐沙班因血药浓度升高和药效影响不应使用[36]。在严重肝功能不全(Child-Pugh C)的患者中，不建议使用 NOACs [37]。考虑到肝功能对抗凝用药的影响，肝硬化患者通常被排除在药物试验之外，临床建议或禁忌症基于少量的证据[38]。

由于部分研究存在其回顾性限制，并且排除部分失代偿期患者，研究的数据质量不高，需要更多前瞻性研究、随机对照试验等高质量数据来支撑。另外拮抗不同凝血因子的 NOACs 是否存在疗效和安全性的差异有待商榷，更需要相关的实验室药物分析和临床研究来证实。

5. 肝硬化合并 PVT 的药物选择

5.1. 利伐沙班

利伐沙班是目前临床上最常用的新型口服抗凝药，它通过抑制 Xa 因子阻止凝血酶原转变成凝血酶而发挥抗凝作用，其抗凝作用与药物浓度密切相关。利伐沙班口服后能够迅速被吸收，口服生物利用度约

为 80%，2~4 h 达到最大血药浓度，在体内与血浆蛋白的结合率较高，约为 95% [39]。2/3 的利伐沙班经肝脏代谢，主要由细胞色素 P450 代谢为约 18 种无活性的代谢产物，一半通过肾脏排出，另一半通过粪便排出；剩下的 1/3 利伐沙班原形经由肾脏排出[40]。其半衰期为 5~9 小时，在年龄较大的患者中可能更长(如 11~13 小时) [41]。与相同代谢途径的强效 CYP3A4/5 和 *p*-糖蛋白酶抑制剂(如利托那韦、酮康唑、伊曲康唑、伏立康唑、泊沙康唑等)合用可使利伐沙班血药浓度平均增加 2.6 倍，显著增加其药效学和出血风险。而与 CYP3A 和 *p*-糖蛋白酶诱导剂(利福平、苯妥英、卡马西平、苯巴比妥等)合用可降低其血药浓度[40]。

利伐沙班是目前研究最多的治疗 PVT 的 NOACs。利伐沙班在美国和欧洲获批用于以下适应症：预防接受择期髋关节或膝关节置换手术的成人发生静脉血栓栓塞；治疗成人深静脉血栓形成、肺栓塞和预防复发；以及预防非瓣膜性房颤成人发生中风和栓塞[42]。Yong Lv 等[43]通过前瞻性队列研究发现，在肝硬化合并 PVT 患者中，长期使用利伐沙班或依诺肝素，相比于 VKA 可降低再血栓形成风险和提高生存期，且不增加出血风险。一项随机对照试验表示，在利伐沙班组中，85% (34/40)的患者在 2.6 ± 0.4 个月内达到了 PVT 完全再通；15%的患者在 6.7 ± 1.2 个月后达到延迟和部分再通，但是明显改善患者腹痛症状、延缓并发症(腹水、门静脉高压、食管静脉曲张出血等)的进展[44]。目前关于利伐沙班的研究较多，证据质量较高，在临床上的使用也非常广泛。但以上研究对象大多为 Child-Pugh A 级或 B 级的患者，缺乏 Child-Pugh C 级患者的相关研究。

5.2. 阿哌沙班

阿哌沙班是一种具有高效、可逆、高选择的直接凝血因子 Xa 抑制剂。阿哌沙班吸收迅速，口服生物利用度约为 50%，服用后 3~4 小时达到最大浓度，血浆蛋白结合高(87%) [45]。它主要通过 CYP3A4 和 CYP3A5 代谢，并且可通过多种途径清除：绝大多数通过粪便排除，27%的阿哌沙班以原形的形式从尿液排出[46]。阿哌沙班的半衰期约为 12 h。与强效 CYP3A4/5 和 *p*-糖蛋白酶抑制剂合用可使阿哌沙班的血药浓度平均增加两倍。相反，阿哌沙班与 CYP3A4/5 和 *p*-糖蛋白酶诱导剂(利福平、苯妥英、卡马西平、苯巴比妥)联合给药可降低其血药浓度[47]。

阿哌沙班主要用于预防房颤患者发生卒中及治疗静脉血栓栓塞疾病。一项比较利伐沙班和阿哌沙班的荟萃分析表明，与利伐沙班相比，阿哌沙班在预防复发性静脉血栓栓塞方面具有相同的疗效，并且可降低大出血和小出血事件的风险[48]。但关于阿哌沙班用于肝硬化合并 PVT 治疗的相关研究仍较少，其有效性和安全性尚需大量循证医学证据。

5.3. 依度沙班

依度沙班是直接凝血因子 Xa 抑制剂，其抗凝机制与利伐沙班类似。依度沙班的生物利用度约为 60%，食物不影响药物吸收，与血浆蛋白结合的比例为 55% [45]。35%的艾多沙班以原形的形式经肾脏排泄；60%则经粪便排出[49]。其半衰期为 10~14 h。依度沙班是 *p*-糖蛋白的底物，强效 *p*-糖蛋白酶抑制剂可使艾多沙班的全身暴露量增加 1.5 至 2 倍[45]。

依度沙班主要用于预防房颤患者发生血栓栓塞并发症和治疗静脉血栓栓塞症[50]。一篇回顾性队列研究纳入了 50 名肝硬化合并 PVT 患者，比较了分别用艾多沙班和华法林治疗 6 个月后的结果，发现艾多沙班组 PVT 体积显著减少，而华法林组 PVT 体积反而显著恶化[51]。但是目前关于依度沙班用于肝硬化合并 PVT 治疗的相关报道非常少，未来尚需大量高质量研究数据验证其有效性和安全性。

5.4. 达比加群酯

达比加群酯属于直接凝血因子 IIa 抑制剂，是一种口服前体药物，生物利用度为 7% [40]。达比加群

酯被机体吸收后迅速转化为有活性的直接凝血酶抑制剂达比加群，它不通过 CYP450 代谢，不诱导或抑制 CYP450。其血浆蛋白结合率为 35% [52]。达比加群是一种 *p*-糖蛋白的底物，因此容易与 *p*-糖蛋白抑制剂或诱导剂发生药物相互作用[53]。主要通过尿路排出(80%~90%)，其半衰期约为 12~17 h [40]。

达比加群主要用于预防非瓣膜性房颤患者发生中风以及预防和治疗成人血栓栓塞疾病。一篇 330 例急性 PVT 患者的回顾性队列研究中，每个 NOACs 组(利伐沙班、阿哌沙班和达比加群)的血栓完全再通率，与依诺肝素组相似，优于华法林组[54]。另外一项研究表明：利伐沙班在肝硬化患者的体外抗凝作用会降低；而达比加群的抗凝作用增强，并且与肝硬化的严重程度成正比[55]。因此关于因子 IIa 抑制剂与因子 Xa 抑制剂对于肝硬化合并 PVT 的疗效是否存在差异值得探讨，相关的研究证据很少。同时达比加群在肝硬化合并 PVT 的证据也不足，需要更多循证医学证据来证实其治疗优势。

6. 小结与展望

肝硬化合并 PVT 的患者应早期诊断、早期开始抗凝治疗，有助于 PVT 再通，预防并发症，提高生存率。最新相关指南和共识建议肝硬化 PVT 患者至少抗凝 6 个月，并可根据患者病情进展、潜在风险等因素延长抗凝时间。利伐沙班、阿哌沙班、依度沙班、达比加群酯等 NOACs 治疗肝硬化合并 PVT 的有效性和安全性已获得一定认可。在临床实践中，NOACs 的选择需要个体化、综合化考虑。由于大多数研究为回顾性分析，循证医学证据不高，未来迫切需要多中心大规模随机对照试验来进一步了解 NOACs 在肝硬化并发 PVT 中的优选药物、适宜疗程，使更多人群获益。

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