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述评 EDITORIAL

不同输注方式对特利加压素安全性及疗效的影响: 当前的争议

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Effect of different infusion approaches on safety and efficacy of terlipressin: Current controversies

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Abstract

Terlipressin, a synthetic analog of vasopressin, has been widely used to treat acute variceal bleeding, hepatorenal syndrome, and other complications of cirrhosis. However, among different infusion approaches of terlipressin, its safety and efficacy are also heterogeneous. Previous studies have demonstrated that continuous infusion of terlipressin is more effective with a lower incidence of adverse events than intermittent intravenous infusion. This paper aims to review the relevant literature and summarize the data regarding the safety and effectiveness of different infusion approaches of terlipressin to guide clinical practice.

Key Words: Terlipressin; Intravenous infusion; Cirrhosis; Acute variceal bleeding; Hepatorenal syndrome; Refractory ascites; Septic shock

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摘要

特利加压素是血管加压素的一种人工合成类似物, 已被广泛用于治疗急性静脉曲张破裂出血及肝肾综合征等肝硬化并发症. 然而, 特利加压素的不同输注方式可能会造成其疗效和安全性有所差异. 既往研究证明持续输注特利加压素比间歇静脉推注更有效且不

良事件发生率更低. 本文着重回顾相关文献并总结特利加压素不同输注方式之间疗效和安全性的差异, 以指导临床实践.

关键词: 特利加压素; 静脉输注; 肝硬化; 急性静脉曲张破裂出血; 肝肾综合征; 难治性腹水; 感染性休克

核心提要: 特利加压素已被广泛用于治疗急性静脉曲张破裂出血及肝肾综合征等肝硬化并发症, 但其最佳输注方式及剂量当前仍存有争议. 本文着重回顾文献并总结特利加压素不同输注方式之间的疗效和安全性的差异, 以指导临床实践.

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0 引言

肝硬化是全球肝病患者死亡的主要病因, 影响着全球1.2亿多人, 常见的危险因素包括酒精滥用、病毒性肝炎和非酒精性脂肪肝等[1]. 肝硬化患者常存在门静脉高压及高动力循环且伴有全身性炎症, 这进一步扩张内脏血管, 减少了有效循环容量. 当缺乏有效干预措施时, 肝硬化将由代偿期进展至失代偿期, 最终导致腹水、肝肾综合征(hepatorenal syndrome, HRS)、食管胃静脉曲张破裂出血以及肝性脑病等并发症[2,3].

特利加压素是一种人内源性血管加压素的人工合成类似物, 以赖氨酸替代内源性加压素肽链中第8位精氨酸, 同时在半胱氨酸处增添了由3个甘氨酸组成的氨基酸支链[4], 能非选择性激动V_1(内脏动脉血管平滑肌)和V_2(肾小管集合管)受体, 但与V_1受体的亲和力是V_2的6倍[5]. 当作用于V_1受体时, 可收缩内脏及外周血管, 减少内脏血流, 从而降低门静脉压(portal venous pressure, PVP), 升高平均动脉压(mean arterial pressure, MAP); 另外, 还可以增加肾血流量及尿量, 进而改善肾功能[6]. 特利加压素分布半衰期为8 min, 静脉给药后约10 min达到峰值浓度, 主要通过代谢物赖氨酸血管加压素(lysine-vasopressin, LVP)发挥作用[5]; 作为一种前药, 肽链外切酶的代谢使其持续释放LVP, 进而延长作用时间. LVP的活性在60 min-120 min时达到峰值, 并在180 min-240 min内保持代谢活性[7]. 特利加压素消除半衰期为50 min, 且药物的清除率随着血药浓度的增加而增加, 这可能导致间歇推注后疗效迅速减弱, 不能长时间维持疗效, 特利加压素血药浓度的急剧增加也可能会引发严重不良事件[8]. 尽管特利加压素目前已被广泛用于治疗急性静脉曲张破裂出血(acute variceal bleeding, AVB)及HRS等肝硬化并发症. 但其最佳输注方式及剂量仍存有争议. 本文主要通过回顾相关文献并总结特利加压素不同输注方式治疗AVB、1型HRS(HRS-1)、难治性腹水及感染性休克的疗效和安全性差异.

1 特利加压素输注方式对AVB治疗的影响

AVB是肝硬化患者常见且致命的并发症, 短期死亡率高达20%-30%[9]. 肝硬化患者发生急性上消化道出血时, 需怀疑AVB[10]. AVB患者应尽早使用特利加压素、生长抑素或奥曲肽[11]. 特利加压素主要作用于内脏循环动脉平滑肌V_1受体, 降低内脏循环容量和门静脉压力, 进而控制AVB[10]. 一项纳入了30项随机对照试验的荟萃分析发现, 与无血管活性药物治疗相比, 特利加压素能显著降低院内死亡率(OR = 0.31, P = 0.008); 然而, 特利加压素与垂体后叶素、生长抑素和奥曲肽在控制出血方面无统计学差异[12]. 2019年, 一项网状荟萃分析发现, 与奥曲肽、生长抑素和血管加压素等血管活性药物相比, 特利加压素能显著降低输血率及再出血风险[13]. 亚太肝病学会推荐AVB患者首选特利加压素, 以2 mg/4 h的剂量治疗2 d-5 d[14]. 欧洲肝病学会推荐特利加压素以2 mg/4 h的剂量输注48 h, 随后改为1 mg/4 h[11]. 然而, 大剂量间歇推注特利加压素不足以长期维持疗效, 且可能增加严重不良事件发生风险.

2013年, Ding等[8]将接受经颈静脉肝内门体分流术(transjugular intrahepatic portosystemic shunt, TIPS)的患者随机分配为间歇静脉推注组(首剂静脉推注2 mg, 随后每6 h推注1 mg; n = 10)和持续泵注组(首剂静脉输注1 mg, 随后每24 h微泵注射4 mg; n = 10), 两组患者均在TIPS术后注射特利加压素并通过门静脉导管直接测量PVP, 持续泵注特利加压素可稳定降低PVP且无严重不良反应, 而间歇静脉推注组降低PVP数小时后会反弹; 输注1 h后, 两组均能降低心率、升高MAP, 但间歇静脉推注组的心率及MAP波动更大; 持续泵注特利加压素对PVP的影响更大. 2018年, 基于上述研究结果, Jha等[15]将86例门静脉高压并发食管静脉曲张出血(esophagogastric variceal bleeding, EVB)的患者随机分为持续输注组(首剂静脉输注1 mg, 随后每天持续输注4 mg; n = 43)和间歇静脉推注组(首剂推注2 mg, 随后每6 h推注1 mg; n = 43), 两组均持续治疗5 d, 两组6 wk内死亡率无统计学差异(18.6% *vs* 9.3%, P>0.05); 但间歇静脉推注组有20.7%的患者治疗失败, 显著高于持续输注组(20.7 *vs* 4.7%, P = 0.02). 然而, 由于患者及医疗环境的限制, 这两项研究并未测量肝静脉

压力梯度(hepatic venous pressure gradient, HVPG).

HVPG>5 mmHg提示窦性门静脉高压症[16]; 在病毒和酒精性肝硬化患者中, HVPG>10 mmHg是静脉曲张等失代偿事件的危险因素, HVPG>12 mmHg是静脉曲张出血的危险因素[17], HVPG>20 mmHg会使再出血等不良预后的风险增加5.21倍[18]. 早在1997年, 有研究发现间歇推注特利加压素并不能降低HVPG[19]. 基于此, Arora等[20]进行了一项单中心随机双盲对照试验, 将110例EVB患者随机分为间歇静脉推注组(2 mg/4 h)和持续输注组(4 mg/24 h), 初始止血后患者行内镜下静脉曲张套扎术并静脉推注2 mg特利加压素, 导管留置24 h, 分别在12 h及24 h后再次测量HVPG, 间歇静脉推注和持续输注特利加压素均能显著降低HVPG, 但持续输注组HVPG应答者更多(85.4% *vs* 58.2%, P = 0.002), 所需平均输注剂量也更低(4.25 mg/dL±1.26 mg/dL *vs* 7.42 mg/dL±1.42 mg/dL); 特利加压素可能会导致腹泻、腹痛、心房颤动、发绀、胸痛、室性早搏和高血压等不良事件, 其中间歇推注组因不良反应需要减少剂量或停药的患者比率显著高于持续输注组(56.4% *vs* 36.3%, P = 0.03).

目前指南推荐间歇静脉推注特利加压素治疗AVB[11,14], 但间歇推注并不能保证24 h内稳定降低PVP, 且MAP频繁波动, 故不利于控制AVB并预防早期再出血. 此外, 大多数患者不能耐受这种高剂量的输注方式, 特别是肝硬化晚期并发静脉曲张出血的患者. 相反, 低剂量持续输注或泵注能有效降低肝硬化患者的HVPG, 进而可能减少不良事件. 因此, 持续输注特利加压素可能更适合治疗AVB.

2 特利加压素输注方式对HRS治疗的影响

HRS是失代偿期肝硬化常见的严重并发症之一, 5年内发病率约为40%, 确诊后生存率仅为5%-20%[21]. 2015年, 国际腹水学会重新修订了AKI(acute kidney injury, AKI)及HRS的定义, 并将HRS-1更名为HRS-AKI[22]. 肝硬化患者会出现内脏血管扩张, 进而降低有效循环容量、全身血管阻力和MAP, 这会激活神经体液系统, 收缩肾血管, 降低肾血流量及肾小球滤过率(GFR), 最终导致扩容无效的肾前性肾损伤(即HRS-AKI)[23].

美国和欧洲指南均建议特利加压素作为HRS-1的一线治疗药物[23]. 特利加压素可作用于V_1和V_2受体, 诱导神经体液系统失活, 进而增加有效循环容量、改善肾脏灌注[13]. Boyer等[24]比较了在白蛋白的基础上加用特利加压素与安慰剂对肝硬化患者肾功能的影响, 特利加压素组(1 mg/6 h)的患者血清肌酐(Scr)降低了1.1 mg/dL; 而安慰剂组的患者Scr仅降低了0.6 mg/dL(P<0.001); 特利加压素能更有效地改善肝硬化患者的肾功能. 2018年, 一项纳入了16项随机对照试验的网状荟萃分析发现, 特利加压素联合白蛋白可有效逆转HRS-1, 改善HRS-1患者的短期生存率[25]. 2021年, Wong等[26]将300例HRS-1患者随机分为白蛋白联合特利加压素组和单用白蛋白组(每5.5 h-6.5 h静脉输注1 mg特利加压素, 治疗持续14 d), 与安慰剂相比, 特利加压素联合白蛋白能更有效地逆转HRS-1(32% *vs* 17%, P = 0.006). 基于此, 美国食品药品监督管理局批准了特利加压素用于治疗HRS.

欧洲肝病学会推荐特利加压素治疗HRS-1的初始剂量为0.5-1 mg/4-6 h, 若Scr较基线减少<25%, 则逐步增至2 mg/4-6 h[11]. 美国胃肠病学会推荐特利加压素治疗HRS-1的起始剂量为1 mg/4-6 h, 若3 d内Scr较基线降低≤25%, 则剂量增至2 mg/4-6 h; 特利加压素除间歇静脉推注外, 也可以2 mg/d的起始剂量持续静脉输注, 每24-48 h逐渐增加剂量, 增至最大剂量12 mg/d或HRS逆转. 两种输注方式的疗效相似, 但持续输注组的累积日剂量较低, 这可能会减少不良反应发生的风险[27]. 2009年, Gerbes等[28]发现在白蛋白的基础上持续输注特利加压素可以使42%的患者实现HRS逆转, 仅有9%的患者出现心律失常; 相比于既往间歇推注的研究, 逆转率更高且心血管不良事件发生率更低[29,30]. 2016年, Cavallin等[31]将71例肝硬化并发HRS-1的患者随机分为持续静脉泵注组(2 mg/d; n = 34)和间歇静脉推注组(0.5 mg/4 h; n = 37), 两组治疗应答率及90 d无移植生存期无统计学差异; 但持续泵注组不良事件发生率(35.29% *vs* 62.16%, P<0.025)低于间歇静脉推注组, 其中, 严重不良事件发生率(21% *vs* 43%, P<0.05)更低; 完全缓解(55.88% *vs* 45.95%)和部分缓解率(20.59% *vs* 18.9%)均高于间歇静脉推注组; 持续泵注组逆转HRS所需的剂量更低(2.23 mg/d±0.65 mg/d *vs* 3.51 mg/d±1.77 mg/d, P<0.05), 且能更持久地降低PVP.

CONFIRM研究发现39.5%的患者在应用特利加压素治疗后发生了急性呼吸衰竭、呼吸困难、缺氧、胸腔积液和肺水肿等呼吸系统不良事件, 而安慰剂组仅有25.3%; 更重要的是, 特利加压素组有22例患者(11%)90 d内死于呼吸系统疾病; 相比之下, 安慰剂组仅有2(2%)例患者[26]. 值得注意的是, 该研究采用间歇静脉推注, 且剂量较大. 相比之下, 持续输注或泵注引起的呼吸系统不良事件很罕见. Arora等[32]将120例慢加急性肝衰竭患者随机分为持续输注特利加压素(2-12 mg/d; n = 60)或去甲肾上腺素(0.5-3.0 mg/h; n = 60)组, 两组均未发生呼吸系统不良事件.

综上, 持续输注或泵注特利加压素治疗HRS-1的疗效与间歇静脉推注相近, 而持续输注所需剂量及不良事件发生率更低, 故未来可考虑持续输注特利加压素治疗HRS-1.

3 特利加压素输注方式对难治性腹水治疗的影响

腹水是失代偿期肝硬化患者最常见的并发症[33]. 肝硬化合并腹水的患者中约5%-10%为难治性腹水, 难治性腹水患者6 mo生存率仅为50%. 目前治疗措施包括大容量腹腔穿刺联合人血白蛋白、TIPS、肝移植、血管收缩剂和自动低流量腹水泵[34]. 难治性腹水患者常伴有HRS, 特利加压素可显著改善GFR、Scr、肾血流量和尿量, 故可用于辅助治疗[35]. 中国肝硬化腹水及相关并发症的诊疗指南推荐特利加压素用于治疗肝硬化顽固型腹水, 每12 h静脉缓慢推注(至少15 min)或持续静脉点滴1 mg-2 mg, 有应答者持续应用5 d-7 d; 无应答者, 可每6 h静脉缓慢推注或持续静脉点滴1 mg-2 mg. 停药后病情反复, 可再重复应用[36]. 但目前尚无研究比较特利加压素不同输注方式治疗难治性腹水的疗效及安全性差异, 未来仍需高质量研究加以证明.

4 特利加压素输注方式对感染性休克治疗的影响

脓毒症引起的感染性休克每年影响着数百万人[37], 其死亡率高达40%-50%[38]. 感染性休克患者会出现有效循环容量下降和组织灌注不足, 故液体复苏至关重要[39]. 然而, 许多患者经充分液体复苏后仍存在持续性低血压, 需应用血管活性药物以维持MAP[40]. 去甲肾上腺素(norepinephrine, NE)为治疗感染性休克的一线血管活性药物[41]. 然而, 感染性休克患者对儿茶酚胺类药物的敏感性会随时间逐渐降低[6], 从而需要更高剂量的NE来维持稳定的MAP, 这可能会增加不良事件的发生率[42]. 指南推荐, 应用NE后仍存在低血压的感染性休克患者可考虑加用血管加压素[37], 但血管加压素不具有选择特异性, 其激活V_1受体时, 也会激活其他受体, 从而导致血小板减少、低钠血症及高胆红素血症等不良反应[43]. 与血管加压素不同, 特利加压素对V_1受体亲和力显著高于其他受体. 因此, 当感染性休克患者应用NE后仍存在低血压时, 加用特利加压素可能更合适. 近期一项随机对照试验将84例肝硬化合并感染性休克的患者随机分为NE单药治疗组和NE联合特利加压素组. 联合组有93%的患者MAP能维持在65 mmHg以上, 而单药组仅有69%; 与单药组相比, 联合组的不良事件发生率更高, 主要是手指缺血[44]. 值得注意的是, 该试验采用间歇静脉推注特利加压素, 长时间大剂量间歇静脉推注可能导致血管过度收缩, 进而减少全身血流量和氧转运量[45]. 既往动物试验发现, 与间歇推注特利加压素(1 mg/6 h)相比, 持续输注(2 mg/d)能更有效地逆转低血压并改善心肌、肾和肝功能[46,47]. 尚无临床研究探讨持续输注特利加压素对感染性休克患者的疗效和安全性, 未来需要更多大型、高质量研究加以分析.

5 结论

特利加压素已被推荐作为肝硬化伴AVB或HRS-1的一线治疗药物. 与间歇静脉推注相比, 持续输注特利加压素能持久、稳定地降低PVP. 此外, 持续输注所需的药物剂量更小, 不良事件发生率更低且患者耐受性也更好, 故未来可考虑持续输注特利加压素治疗AVB及HRS-1. 然而, 持续输注特利加压素治疗难治性腹水和感染性休克疗效和安全仍未知, 需高质量研究进一步探讨.

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