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述评 EDITORIAL

特利加压素治疗肝肾综合征的循证医学依据

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摘要

肝肾综合征(hepatorenal syndrome, HRS)是肝硬化的严重并发症之一, 主要表现为少尿、尿钠潴留和血清肌酐升高. 肝移植是治疗肝肾综合征的最佳方式, 但仅有少部分患者进行了肝移植. 目前药物治疗方式主要为血管收缩剂联合白蛋白. 特利加压素是一种人工合成的血管加压素类似物, 主要用于治疗肝肾综合征. 本文旨在从循证医学角度回顾特利加压素治疗HRS的当前现状.

Key Words: 特利加压素; 肝肾综合征; 肝硬化; 去甲肾上腺素; 临床试验

Current evidence regarding terlipressin for treatment of hepatorenal syndrome

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Abstract

Hepatorenal syndrome (HRS) is a serious complication of liver cirrhosis, which is characterized by oliguria, severe urinary sodium retention, and elevated serum creatinine levels. Liver transplantation is the best choice of therapy, but is rarely available. Current mainstay pharmacological therapy is vasoconstrictors with albumin. Terlipressin is a synthetic analog of vasopressin, and it has been used for the treatment of HRS. This article reviews the current status regarding terlipressin in the management of HRS from the perspective of evidence-based medicine.

Key Words: Terlipressin; Hepatorenal syndrome; Liver cirrhosis; Noradrenaline; Clinical trial

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关键词: 特利加压素; 肝肾综合征; 肝硬化; 去甲肾上腺素; 临床试验

核心提要: 目前, 血管活性药物联合白蛋白是肝肾综合征(hepatorenal syndrome, HRS)的主要药物治疗手段. 循证医学证据显示,特利加压素联合白蛋白可有效改善HRS患者的肾功能.

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0 引言

肝肾综合征(hepatorenal syndrome, HRS)是肝硬化的致命性并发症之一[1-3], 同时也是一种特殊类型的急性肾损伤[4]. 根据国际腹水委员会, 将肝肾综合征分为两类, 即Ⅰ型肝肾综合征(Hepatorenal syndrome Ⅰ, HRS Ⅰ)与Ⅱ型肝肾综合征(Hepatorenal syndrome Ⅱ, HRS Ⅱ). HRS Ⅰ的特点为进展迅速、预后较差, HRS Ⅱ的特点为进展缓慢、预后相对较好[5]. HRS治疗方法[6]包括肝移植[7]、经颈静脉肝内门腔静脉分流术[8]和血管活性药物[9](如特利加压素[10]、去甲肾上腺素、多巴胺和奥曲肽)联合白蛋白. 特利加压素[11-13]主要用于治疗急性静脉曲张破裂出血[14,15]和肝肾综合征, 与血管平滑肌细胞的V1受体结合, 收缩血管, 减少门静脉的血流, 降低门静脉的压力[16]. 特利加压素可降低肾素浓度, 减少血管紧张素Ⅱ产生, 减轻肾脏血管收缩, 增加肾脏血流灌注, 显著增加肾小球滤过率, 增加尿钠排泄[17]. 特利加压素治疗期间可发生的不良反应[18]主要有胃肠道症状、低钠血症[19,20]、皮肤缺血[21]或坏死和心、肺栓塞等. 本文简要回顾特利加压素治疗HRS的临床试验证据.

1 特利加压素联合白蛋白与白蛋白或安慰剂联合白蛋白比较

目前, 有5项随机对照试验比较了特利加压素联合白蛋白与单独应用白蛋白或安慰剂联合白蛋白治疗HRS的疗效. Neri等[22]发现了特利加压素联合白蛋白组(n = 26)肌酐改善显著优于单独应用白蛋白组(n = 26)(P<0.001)(特利加压素组治疗后112 μmol/L±32 μmol/L; 单独应用白蛋白组治疗后188 μmol/L±43 μmol/L), 且特利加压素联合白蛋白组的生存率较单独应用白蛋白组更高(P<0.0001). Martin-Llahi等[23]也发现了对于HRS患者, 特利加压素联合白蛋白组(n = 23)肾功能改善比率显著优于单独应用白蛋白组(n = 23)(43.5% *vs* 8.7%, P = 0.017), 但两组3 mo生存率无显著差异(27% *vs* 19%, P = 0.7).

Sanyal等[24]比较了特利加压素联合白蛋白与安慰剂联合白蛋白对HRS Ⅰ的疗效. 结果显示, 特利加压素联合白蛋白组(n = 56)肌酐改善显著优于安慰剂组(n = 56)(-0.7 mg/dL *vs* 0 mg/dL, P<0.009), 且HRS Ⅰ逆转率显著优于安慰剂组(34% *vs* 13%, P = 0.008); 尽管特利加压素联合白蛋白组治疗成功率较安慰剂组更高, 但无显著差异(25% *vs* 12.5%, P = 0.093); 两组的不良反应发生率相似. Solanki等[25]发现, 特利加压素联合白蛋白组(n = 12)较安慰剂组(n = 12)尿量显著增加(P<0.05)(特利加压素组治疗后1068 mL/24 h±56 mL/24 h; 安慰剂组治疗后291 mL/24 h±45 mL/24 h), 肌酐清除率显著改善(P<0.05)(特利加压素组治疗后35 mL/min±2.8 mL/min; 安慰剂组治疗后9.3 mL/min±1.7 mL/min), 平均动脉压显著增加(P<0.05)(特利加压素组治疗后95 mmHg±1.6 mmHg; 安慰剂组治疗后70 mmHg±1.4 mmHg), 15 d生存率显著增加(41.7% *vs* 0%, P<0.05). Boyer等[26]发现, 特利加压素联合白蛋白组(n = 97)HRS Ⅰ完全逆转率高于安慰剂组(n = 99), 但无显著差异(19.6% *vs* 13.1%, P = 0.22); 较安慰剂组肌酐显著降低(肌酐降低的平均值: 1.1 mg/dL *vs* 0.6 mg/dL, P<0.001); 两组总体生存率相似. 由此可见, 特利加压素联合白蛋白可有效改善HRS患者的肾功能.

但是, 这些研究仍有一定的局限性, 需要更大样本量的随机双盲试验探讨特利加压素的疗效, 以及特利加压素在不同剂量、疗程情况下的疗效.

2 特利加压素联合白蛋白与去甲肾上腺素联合白蛋白比较

去甲肾上腺素是一种儿茶酚胺, 主要具有α-肾上腺素能活性, 使内脏动脉血管收缩, 从而改善循环功能, 静脉给药后起效迅速[27]. 目前, 有7项随机对照试验比较了特利加压素与去甲肾上腺素治疗HRS的疗效.

Sharma等[28]比较了特利加压素与去甲肾上腺素治疗HRS Ⅰ的疗效. 结果显示, 特利加压素组(n = 20)和去甲肾上腺素组(n = 20)血肌酐水平均显著降低(P<0.05)(特利加压素组治疗后1 mg/dL±0.4 mg/dL; 去甲肾上腺素组治疗后1.2 mg/dL±0.5 mg/dL), 肌酐清除率均显著升高(P<0.05)(特利加压素组治疗后59.8 mL/min±14.2 mL/min; 去甲肾上腺素组治疗后54.9 mL/min±27.5 mL/min), 平均动脉压和尿量均显著增加; 两组肾素活性均降低, 但无显著差异; 特利加压素组有1例严重不良反应. Goyal等[29]也发现, 特利加压素组(n = 20)与去甲肾上腺素组(n = 21)HRS Ⅰ逆转率无显著差异(45% *vs* 47.6%, P = NS); 两组血肌酐水平均显著降低, 平均动脉压

均显著增加; 两组均无严重不良反应. Ghosh等[30]的研究提示, 特利加压素组(n = 23)和去甲肾上腺素组(n = 23)HRS Ⅱ逆转率无差异(73.9% *vs* 73.9%, P = NS); 两组90 d的死亡率也无差异(65% *vs* 61%, P = NS); 两组均无严重不良反应. Singh等[31]同样发现, 特利加压素组(n = 23)和去甲肾上腺素组(n = 23)HRS Ⅰ逆转率无显著差异(39.1% *vs* 43.4%, P = 0.764); 两组15 d死亡率无差异; 两组均无严重不良反应. Alessandria等[32]发现, 特利加压素组(n = 10)与去甲肾上腺素组(n = 12)HRS逆转率无显著差异(83% *vs* 70%, P = NS), 均可显著改善肾脏和循环功能; 两组均无严重不良反应. Saif等[33]发现, 特利加压素组(n = 30)HRS逆转率为57%, 去甲肾上腺素组(n = 30)HRS逆转率为53%. 两组在降低血肌酐、增加尿量方面均无差异. 这些研究表明, 特利加压素和去甲肾上腺素治疗HRS效果相当.

最近, Arora等[34]比较了特利加压素与去甲肾上腺素治疗慢加急性肝衰竭合并肝肾综合征的疗效. 与去甲肾上腺素组(n = 60)相比, 特利加压素组(n = 60)第4 d(26.1% *vs* 11.7%, P = 0.03)和第7 d(41.7% *vs* 20%, P = 0.01)应答率更高; 特利加压素组HRS逆转率更高(40% *vs* 16.7%, P = 0.04); 特利加压素组中需肾脏替代治疗的比率显著降低(56.6% *vs* 80%, P = 0.006); 特利加压素组中28 d生存率明显改善(48.3% *vs* 20%, P = 0.001); 特利加压素组中限制药物使用的不良反应发生率更高(23.3% *vs* 8.3%, P = 0.02). 这项研究表明, 特利加压素联合白蛋白治疗慢加急性肝衰竭合并肝肾综合征的疗效可能优于去甲肾上腺素联合白蛋白.

目前多数研究显示特利加压素与去甲肾上腺素的疗效是相近的. 然而, 最近的研究发现在慢加急性肝衰竭合并肝肾综合征患者中特利加压素的疗效可能更佳.

3 特利加压素联合白蛋白与多巴胺联合呋塞米及白蛋白比较

小剂量多巴胺主要作用于多巴胺受体, 使肾及肠系膜血管扩张, 使肾血流量及肾小球滤过率增加, 尿量及钠排泄量增加. 静脉滴入后体内分布广泛, 5 min内起效[35]. 目前, 仅有1项随机对照试验比较了特利加压素联合白蛋白与多巴胺联合呋塞米及白蛋白治疗HRS的疗效.

Srivastava等[36]比较了特利加压素联合白蛋白和多巴胺联合呋塞米及白蛋白治疗HRS的疗效. 对于HRS Ⅰ患者, 特利加压素联合白蛋白组(n = 20)和多巴胺联合呋塞米及白蛋白组(n = 20)24 h尿量和尿钠均显著增加, 血清肾素活性均显著降低; 两组15 d的生存率无差异(21% *vs* 20%, P = NS); 两组1 mo的生存率也无差异(15.7% *vs* 15%, P = NS). 对于HRS Ⅱ患者, 特利加压素联合白蛋白组(n = 20)和多巴胺联合呋塞米及白蛋白组(n = 20)24 h尿量和尿钠均显著增加, 血清肾素活性均显著降低; 两组15 d的生存率无差异(47% *vs* 65%, P = NS); 两组1 mo的生存率也无差异(35% *vs* 31%, P>0.2). 两组均无严重不良反应. 研究提示, 特利加压素联合白蛋白和多巴胺联合呋塞米及白蛋白治疗HRS疗效相当.

4 特利加压素联合白蛋白与奥曲肽联合米多君及白蛋白比较

奥曲肽为生长抑素类似物, 可降低内脏血流. 米多君为α1肾上腺素受体激动剂, 可使血管收缩[37]. 目前, 仅有1项随机对照试验比较了特利加压素联合白蛋白与奥曲肽联合米多君及白蛋白治疗HRS的疗效.

Cavallin等[38]比较了特利加压素联合白蛋白和奥曲肽联合米多君及白蛋白治疗HRS的疗效. 特利加压素组(n = 27)逆转肾功能方面显著优于(70.4% *vs* 28.6%, P = 0.01)奥曲肽联合米多君及白蛋白组(n = 22); 两组1 mo的生存率无显著差异(70% *vs* 67%, P = NS); 两组3 mo的生存率也无显著差异(59% *vs* 43%, P = NS). 特利加压素组有1例严重不良反应. 总的来说, 这项研究表明, 特利加压素联合白蛋白改善肾功能的效果优于奥曲肽联合米多君及白蛋白.

5 有关特利加压素治疗肝肾综合征的荟萃分析

目前有12项关于特利加压素治疗HRS的荟萃分析[39-50], 本文主要简述5项研究的结果. Israelsen等[42]系统评价了10项研究以探讨特利加压素治疗HRS的疗效和安全性. 特利加压素和其他血管活性药物在治疗应答、死亡率和严重不良反应事件(RR = 0.96)等方面无差异. Nanda等[40]系统评价了13项研究; 特利加压素较安慰剂(OR = 4.72, P<0.003)、米多君联合奥曲肽(OR = 5.94, P<0.005)更有效. 特利加压素与去甲肾上腺素相比无统计学差异. Sridharan等[39]系统评价了16项研究; 特利加压素和去甲肾上腺素均可逆转HRS(OR = 6.65和6.81), 但死亡率无显著差异(OR = 0.6). Zheng等[41]系统评价了11项研究; 特利加压素可有效逆转HRS Ⅰ、降低短期死亡率, 但不良反应较去甲肾上腺素更多. 李慧等[43]发现, 特利加压素联合白蛋白治疗HRS Ⅰ较单独应用白蛋白可明显提高HRS缓解率、提高生存率、降低血肌酐水平、升高平均动脉压, 但对尿量无明显影响.

6 持续静脉泵入特利加压素与静脉推注特利加压素的比较

Cavallin等[44]比较持续静脉泵入与静脉推注特利加压素对HRS的疗效. 此项随机对照试验结果显示, 持续

静脉泵入特利加压素不良反应发生率显著低于静脉推注(35.29% *vs* 62.16%, P<0.025). 两组治疗有效率无统计学差异(76.47% *vs* 64.85%, P = NS). 持续静脉泵入特利加压素平均日剂量显著低于静脉推注特利加压素(2.23 mg/d±0.65 mg/d *vs* 3.51 mg/d±1.77 mg/d, P<0.05).

7 结论

基于当前临床试验证据, 特利加压素联合白蛋白可有效改善HRS患者的肾功能. 特利加压素联合白蛋白优于奥曲肽联合米多君及白蛋白, 但与去甲肾上腺素联合白蛋白、多巴胺联合呋塞米及白蛋白疗效相似. 已有临床试验仍存在一定的问题, 仍需扩大样本量以验证上述结论. 未来研究需要更全面地分析临床及实验室指标, 如平均动脉压、肾素、醛固酮水平、一氧化氮合成酶水平等, 以比较不同血管活性药物逆转HRS的潜在机制. 日后也需要更多的临床试验探讨延长特利加压素的给药疗程和增加给药剂量在治疗HRS方面的疗效差异.

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