

TIPS术后肝性脑病危险因素的研究进展

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摘要

经颈静脉肝内门体分流术(transjugular intrahepatic portosystemic shunt, TIPS)是一种能够有效缓解门静脉高压的介入治疗技术, 被广泛用于治疗食管胃底静脉曲张出血、顽固性腹水、Budd-Chiari综合征等。肝性脑病(Hepatic encephalopathy, HE)是TIPS术后最为典型的分流相关疾病, TIPS术后肝性脑病(HE)的发生延长了患者的住院天数并降低了患者的生活质量, 所以TIPS术后预防肝性脑病是一项很重要的临床任务。术前评估患者发生肝性脑病的危险因素, 以及找出TIPS术后发生HE的高风险人群, 通过积极预防, 密切随访, 对尽可能实现减少HE的发病率具有重要意义。本文旨在通过对相关文献进行复习来增强临床医生对该病的认识, 为临床医生对肝性脑病的诊断、治疗及预防提供依据。

关键词

经颈静脉肝内门体分流术, 肝性脑病, 危险因素

Research Progress on Risk Factors of Hepatic Encephalopathy after TIPS

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Abstract

Transjugular intrahepatic portosystemic shunt (TIPS) is an interventional therapy technique that can effectively relieve portal hypertension. It is widely used in the treatment of esophageal fundus venous hemorrhage, refractory ascites, Budd-Chiari syndrome, and so on. Hepatic encephalopathy (HE) is the most typical shingal-related disease after TIPS. The occurrence of hepatic encephalo-

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pathy (HE) after TIPS prolongs the length of stay and reduces the quality of life of patients. Therefore, the prevention of hepatic encephalopathy after TIPS is a very important clinical task. Preoperative assessment of the risk factors of patients with hepatic encephalopathy and identification of high-risk groups of HE patients after TIPS are of great significance for reducing the incidence of HE as much as possible through active prevention and close follow-up. The purpose of this paper is to enhance the understanding of the disease by reviewing the relevant literature, and to provide the basis for the diagnosis, treatment and prevention of hepatic encephalopathy.

Keywords

Transjugular Intrahepatic Portosystemic Shunt, Hepatic Encephalopathy, Risk Factors

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1. 引言

《肝硬化肝性脑病诊疗指南》提出[1], 按照原发肝病的类型, 肝性脑病(HE)可分成 A、B、C 三类型, A 型 HE 一般产生于急性肝功能衰竭的基础上, 而 B 型 HE 一般是由于门-体分流所造成, 无明确的肝功能损害; C 类型产生于缓慢肝损害和肝变硬等肝病背景上。本章重点针对 C 类型背景下的 HE 的风险原因展开了讨论。TIPS 手术通过颈静脉入路, 从肝静脉穿刺肝内门静脉, 在肝静脉与门静脉之间建立门-体分流道, 降低门静脉压力[2], 纠正曲张静脉出血及顽固性腹水, 但 TIPS 术后不良事件发生率高, 分为操作相关并发症及分流相关并发症, 限制了其在临床实践中的应用[3], 肝性脑病(HE)是 TIPS 后的主要并发症之一, 有研究发现, TIPS 后, 20%~50%的患者会出现显性 HE 发作[4] [5], 需要注意的是, HE 的发生率与当地医疗技术水平等因素相关, HE 的发生增加了患者的入院次数和医疗费用, 降低了肝硬化患者的生活质量, 因此, 确定 TIPS 术后肝性脑病的风险因素至关重要, 因为这些风险因素可以用于识别 HE 发生的高危患者, 通过对他们进行密切监测和早期干预, 为患者的后续治疗及预后改善提供指导。

现在的许多研究发现患者年龄、术前 HE 发生史、Child-Pugh 分级、血氨水平以及门静脉压力梯度等可以作为术后肝性脑病发生的预测因素, 对此类高危患者进行早期预防可以减少 HE 发生。

2. TIPS 术后肝性脑病的发生机制

肝性脑病发生的机制目前尚未完全阐明, 主流说法是氨中毒学说[6]。TIPS 术后肝性脑病发生的可能原因是门静脉分流后, 一部分血液不经过肝脏的滤过直接进入体循环, 导致肠道细菌产生的氨不容易被肝脏转化为尿素, 从而引发血氨升高[7], 血氨浓度过高可干扰脑内三羧酸循环, 导致脑胶质细胞过度的激活, 使得星形胶质细胞水肿, 从而引起患者感觉、运动、认知等障碍[8]。另外 TIPS 手术后支架的植入会进一步损伤肝实质并导致起血管受压、阻塞, 肝实质和血管损伤可能会导致患者肝脏缺血, 不能有效清除体内毒素进而导致 HE [9]。

3. TIPS 术后肝性脑病的危险因素

3.1. 肝性脑病的非手术相关危险因素

3.1.1. 年龄

Zeng X, Yin C, Sun CY [8]等人的多因素回归分析显示年龄是肝性脑病的独立危险因素, 此外, 一

项探讨肝性脑病发生风险的预测因素的研究证实: 患者年龄较大、MELD 评分较高与 HE 风险显著相关[10]。一个方面, 随着年龄的增长, 患者本身肝功能代偿能力差, 不能有效清除体内毒素, 从而增加肝性脑病的发生风险。此外, 随着年龄的增长, 感官知觉、记忆、注意力等认知能力面临着正常的老化[11], 且血脑屏障的透过性增加, 这使得 TIPS 术后血氨更易透过血脑屏障而引发肝性脑病, 此外高龄患者更易发生便秘而导致肠道细菌产氨增多, 导致肝性脑病的发生。

3.1.2. 实验室指标

1) 血浆氨与血肌酐

氨中毒学说是 HE 的主要发病机制, 那么, TIPS 术后的 HE 是否也与氨中毒有关呢? 研究表明, TIPS 术后病人体内动脉和静脉中血氨水平均增加, 分流术后大量含氨丰富的血浆直接流入人体循环, 引起血浆氨水平迅速增加, 致使 HE 发生, 也有调查显示, TIPS 术后出现 HE 的病人血浆氨浓度明显超过未出现 HE 的病人[8]。此外, 研究证明术前的血清肌酐水平升高是 TIPS 术后 HE 发生的另外一个危险因素[12]。肾功能损害往往提示患者的肝功能进一步减退。长时间的肌酐水平升高会加重毒素蓄积, 进而诱发肝性脑病。

2) 低钠血症

在较早的研究中就已经有人发现低钠血症(HN)是一个促进 HE 发展的危险因素。Merola 等人[13]发现, 术前血钠水平是评估 TIPS 术后一周内发生显性 HE 的预测因素[14], 后来的研究证实了这一点, 并得出结论: 低钠血症的严重程度与 HE 的恶化程度直接相关[15]。低钠血症患者对于利尿剂的敏感性较低, 并且因为肝性脑病、肝肾综合征等原因住院的几率也比较高。

3) 血清白蛋白

Zhaohui 的研究团队得出结论: ALB 水平(OR = 0.878, 95%CI = 0.834~0.924)是发生显性 HE 的独立危险因素[16]。白蛋白主要在肝脏合成, TIPS 术前白蛋白水平降低代表了肝脏的合成功能较差, 此外, 低白蛋白血症加重肝硬化患者的胃肠道淤血, 致肠道细菌产氨增加, 另一方面, 低白蛋白血症也反映了患者营养状况不佳, 以上因素增加了 TIPS 术后肝性脑病的发生风险。

4) 其他化验室指标

陈丽娜等人[17]在关于肝性脑病预测因素的研究中发现, 尿素氮、总胆红素(TBIL)是 TIPS 术后肝性脑病的影响因素。此外, 唐艳芳等人的单因素 Logistic 回归分析发现, 血氨水平高、血清胆碱酯酶水平低、TBIL 水平高、凝血酶原活动度(PTA)降低均是隐形 HE 发生的危险因素(P 均<0.05) [18]。

3.1.3. 肝功能水平

门体分流道的建立减少了肝脏的血液灌注, 造成肝脏养分供应减少, 从而导致肝功能受损, 同时肝功能损害也引起了血氨含量增加, 进而导致 HE 的产生。肝脏体积作为评价肝脏储备功能的指标, 肝脏体积越小, 肝脏的储备能力越差。研究发现肝脏体积在一定程度上能够作为 TIPS 术后发生 HE 的危险因素[19]。已知 Child-Pugh 评分和终末期肝病模型(MELD)评分肝硬化严重程度的常用指标。Liu [20]等人通过研究发现术前较高的 Child-Pugh 和较小的脾脏体积是 TIPS 术后显性 HE 的独立危险因素。MELD 评分系统联合术后血钠水平, 形成 MELD-Na 评分系统, 可用于评估 TIPS 术后患者预后[21], 熊峰[22]的研究发现 MELD、MELD-Na、Child-Pugh 对 TIPS 术后发生显性 HE 预测有一定的准确性。需要注意的是, MELD、MELD-Na 评分在预测 TIPS 术后死亡率方面的应用价值已经被证实[23], 但其是否能够作为 TIPS 术后肝性脑病的风险因素和预测模型尚有争议, 需要更进一步的研究证实。

3.1.4. 肌肉减少和营养不良

肌肉减少症被认为是 tips 后显性 HE 的一个强有力的预测因素[24] [25]。在一项针对接受 TIPS 治疗

肝硬化患者的多中心队列研究中, 作者证实了肌肉少症对 TIPS 后 HE 的发展有负面影响[26]。肌肉减少症是肝硬化患者的常见合并症, 可能与各种原因导致的终末期肝病营养不良状态较差有关, 其患病率高达 30%~70% [27]。骨骼肌能够将氨转化为谷氨酰胺, 谷氨酰胺再转化为尿素随后由肾脏排出[25]。肌肉萎缩时可导致氨解毒功能受损, 导致高氨血症和肝性脑病[28], 最近的一项荟萃分析表明, 肝硬化患者中肌肉减少症和肝性脑病之间存在显著关联[29]。由此可推断, 肌肉减少症患者术前可以通过加强营养、增长肌肉来降低术后肝性脑病的发生风险。

3.1.5. PPI 的应用

一项 meta 分析[30]结果显示, PPI 使用与 HE 风险之间存在显著相关性(OR = 1.50, 95%CI: 1.25~1.75), 但该研究受限于样本数据不够充足。在此基础上 Dai [31]等人研究了质子泵抑制剂与 TIPS 术后肝性脑病的发生率之间的关系, 结果证实: 在一个独立的患者队列中, PPI 的使用与 tips 后新发或恶化的 HE 发生率增加相关。这可能是由于 PPI 的抑酸作用会引起肠道菌群失调、菌群移位, 导致自发性细菌性腹膜炎, 增加 TIPS 术后 HE 发生风险。

3.1.6. 合并糖尿病

近几年的研究发现糖尿病(diabetes mellitus, DM)已成为肝性脑病的又一潜在危险因素。DM 可以通过加速肌肉分解增加氨的产生, 此外, DM 患者全身炎症、胰岛素抵抗、自主神经功能障碍和肠道细菌过度生长等因素均参与增加肝性脑病的发生风险[32]。Labenz [33]通过研究发现糖尿病可能与肝硬化患者出现隐性 HE 和发展显性 HE 的高风险有关。这给我们的启示是在 TIPS 术前管理好患者的血糖可能是降低 HE 风险的有效措施。

除以上因素外, 术前 HE 病史、术前出现亚临床认知功能损伤、门静脉分流、受教育程度低[8]被证实也参与 TIPS 术后 HE 的发生。

3.2. 肝性脑病的手术相关危险因素

3.2.1. 门体静脉压力梯度(PPG)

门体压力梯度即门静脉压力(PVP)与右房压力(RAP)的差值, 分流术后 PVP 下降, RAP 增加, 因此 PPG 下降更多。当 PPG 增加时(高于 12 mmHg), 出血及腹水的风险升高, 当 PPG 下降时(通常指小于 5~10 mmHg 时) [34], 则会增加肝性脑病和肝衰竭的发生风险。门静脉系统梯度(PSG)与分流的程度直接相关, 且 PPG 下降程度越大, 支架内血流越大, 肝性脑病的发生率可能就越高[35], 也有研究发现, tips 后 HE 患者和未接受 HE 患者的 PSG 无显著差异[36]。由此可见, TIPS 术中测量 PPG, 能够较为精准的控制分流的血流量及压力, 从而在保证降低门脉压力、防止再出血的同时, 又能够保证肝脏的灌注, 从而不会导致肝性脑病和肝功能衰竭等重大并发症的出现。近年来, 一种新的 Viatorr 控制扩张内假体[VCX] (W.L. Gore & Associates Inc; Flagstaff, AZ USA)被推出, 其分流直径为 8 mm, 随着时间的推移不会出现明显的被动扩张[37], 这提高了 PPG 的可控性[38], 有利于更准确的测量。已经有研究证实这种内假体能够降低 HE 的发生率[39]。

3.2.2. 术中门静脉穿刺部位及支架直径

目前的研究结果表明与经门静脉右支穿刺比较, 经门静脉左支穿刺病人术后的 HE 风险较低[40]。Luo [41]的研究团队认为门静脉左支主要收集含氮物质较少的脾静脉的血液, 而回流入门静脉右支的肠系膜上静脉血液中含大量蛋白质和氨基酸, 导致血氨浓度较门静脉左支高[42], 因此穿刺门静脉右支时, 门体分流术后更容易并发肝性脑病[43] [44]。Liu 等人的荟萃分析显示: 8 mm 支架置入 TIPS 后 HE 的风险显著低于 10 mm 支架(风险降低 32%), 其再出血/穿刺风险增加 76% [45]。针对不同并发症的最佳支架直径的选择仍然存在争议, 且支架直径与 TIPS 术后肝性脑病的发生风险增加是否相关, 尚未达成共识。

3.2.3. 血流动力学改变

前文提到 10 mm 支架相较于 8 mm 支架更容易发生肝性脑病[45], 这或许与支架内径增宽导致进入体循环的血流量增多有关。TIPS 术后支架内血流量的大小可能与肝性脑病的发生具有相关性, 这一点已经在一些最近的研究中得到证实[46]。肝硬化患者体内存在高动力循环模式, 即心输出量增加, 外周血管扩张, 体循环血管阻力下降, 使得有效循环血量减少[47], 这与肝硬化晚期肝脏合成功能减退及营养物质吸收差, 门静脉系统压力升高、血液瘀滞和分流有关。建立门体分流道之后, 门脉瘀滞血液重新进入体循环, 有效循环血量增加, 分流术后大量血液回流至心脏, 这将导致心腔的容积、肺毛细血管楔压等一过性增大[48], 随着时间的推移, 心脏对 TIPS 术后容量负荷的增加逐渐代偿、适应, 以上指标会恢复至术前状态, TIPS 术后血流动力学的改变是否影响肝性脑病的发生率还需要进一步验证。

4. 总结

近年来, 尽管通过合理的选择分流路径和改变内径支架的使用, TIPS 术后 HE 的发生率已明显降低, 但 TIPS 术后 HE 的发病率却仍居高不下, 影响了 TIPS 的长期效果。TIPS 术后 HE 的发生是影响患者预后最重要的因素, 严重影响患者的生存质量, 也给患者带来了经济负担。因此, 明确 TIPS 术后肝性脑病的危险因素, 通过早期干预能够显著降低其发生率。本文综述了 TIPS 术后可能引发或促进 HE 发生的危险因素, 以指导临床工作者对术前、术中和术后各种影响 HE 发生的因素进行更好地管控, 从而降低 TIPS 术后肝性脑病的发生率。

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