·综 述 General review·

经颈静脉肝内门体分流术后肝性脑病预后因素研究进展

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【摘要】 1988 年经颈静脉肝内门体分流术(TIPS)首次临床应用以来,TIPS 相关理论和技术日益完善。然而术后肝性脑病(HE)发生仍是限制其临床广泛应用的主要并发症。因此,掌握 TIPS 术后 HE 发生的预后因素,可有效预防其发生。既往已有许多 TIPS 术后 HE 预后因素的报道,包括患者年龄、术前 HE 发生史、Child–Pugh 分级、血氨水平、门静脉压力梯度等。本文主要就 TIPS 术后 HE 预后因素最新研究进展及本中心经验作一综述。

【关键词】 经颈静脉肝内门体分流术; 肝性脑病; 预后因素

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Research progress in studying the prognostic factors of hepatic encephalopathy occurring after transjugular intrahepatic portosystemic shunt

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【Abstract】 Objective Since the first clinical application of transjugular intrahepatic portosystemic shunt(TIPS) in 1988, the theories and techniques related to TIPS have become increasingly perfect. However, post-TIPS hepatic encephalopathy(HE) has been a major complication that limits its widespread use in clinical practice. Therefore, a full understanding of the prognostic factors for post-TIPS HE can effectively prevent its occurrence. There have already been many reports concerning the prognostic factors for post-TIPS HE so far. These reports have analyzed and investigated the risk factors for post-TIPS HE, including patient age, history of preoperative HE, Child-Pugh grade, blood ammonia level, portal vein pressure gradient, etc. This paper aims to provide a detailed review about the latest progress in the research of prognostic factors for post-TIPS HE and to summarize the clinical experience in dealing with post-TIPS HE at authors' medical center. (J Intervent Radiol, 2022, 31: 301-306)

【Key words】 transjugular intrahepatic portosystemic shunt; hepatic encephalopathy; prognostic factor

经颈静脉肝内门体分流术(transjugular intrahepatic portosystemic shunt,TIPS)是治疗门静脉高压并发症的有效方法[1]。然而术后主要并发症有肝性脑病(hepatic encephalopathy,HE)和支架阻塞引起门体分流功能障碍。有研究报道 10%～50%门静脉高压患者接受 TIPS 治疗后会发生 HE[2]。一旦发生 HE,只能给予相应措施改善患者症状,如降低血氨水平、消除诱因等。因此,了解 HE 预后因素,有助于临床早期预防和治疗,使临床医师更加合理地选择 TIPS 适宜人群。本文主要就 TIPS 术后 HE 预后因素研究进展及本中心经验作一综述。

1 HE 分级、临床表现和诊断

HE 是由肝功能失代偿和/或门体静脉异常分流所导致的大脑神经功能障碍,表现为从亚临床改变到昏迷的广谱神经或精神异常[3]。HE 临床表现具有

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多样性,发病初期仅表现为注意力、记忆力降低或脑电生理异常,随着疾病进展可出现嗜睡、谵妄,甚至昏迷等神经精神功能紊乱症状[4]。根据临床表现,HE 可分为隐匿性肝性脑病(covert hepatic encephalopathy,CHE)和显性肝性脑病(overt hepatic encephalopathy,OHE)两大类。West-Haven 分级标准将 HE 分为 0～4 级,CHE 包括其中 0、1 级,OHE 包括其中 2～4 级[3]。

目前 HE 诊断主要依据急性肝衰竭、肝硬化和/或门体分流病史、神经精神异常表现及特殊辅助检查,并排除其他原因所致的神经精神异常。

2 TIPS 手术及术后门静脉压力梯度改变

2.1 术中门静脉穿刺位置

有研究显示,与经门静脉右支穿刺相比,经门静脉左支穿刺患者术后 HE 发生率更低,并延长长期生存率[5]。Luo 等[6]研究认为门静脉左支主要收集来自脾静脉的血液,由于不直接引流经肠系膜上静脉回流的富含蛋白质和氨基酸的血液,血氨浓度较门静脉右支低,因此穿刺门静脉左支行分流时进入体循环的氨浓度与直接穿刺右支相比较低,而血氨升高是引发 HE 的重要诱因。但本中心在临床 TIPS 术中脾静脉、肠系膜上静脉造影和术前 CT 静脉造影(CTV)成像中均发现肠系膜上静脉血流并不一定主要流向门静脉右支,脾静脉血流同样也不一定主要流向门静脉左支。推测可能与门静脉主干与脾静脉、肠系膜上静脉三者间血流角度有关系,当然脾静脉与肠系膜上静脉两者间流量比例也有一定关系。由于个体差异,部分患者适合门静脉左支分流,部分患者则适合门静脉右支分流,因此未来可以就如何在接受 TIPS 治疗患者中个体化选择门静脉穿刺位置进行探索。

2.2 支架直径

研究表明,门体分流支架直径大于 8 mm 是术后发生 HE 的独立危险因素,并且支架尺寸大小与术后 HE 发生风险高低呈正相关[7-8]。术后 HE 发生可能与分流血液量及门静脉压力梯度相关,这与支架直径大小相关[9]。门静脉主要接受含氨丰富的肠系膜上静脉血液回流,因此支架直径越大,门体分流血液量越多,体循环血液中氨水平越高,术后 HE 发生率越大[6]。此外,支架直径越大,门静脉压力梯度下降越明显[9],流经肝脏的血量随之降低,肝功能可能受到影响。Cui 等[10]研究显示,分流支架从小直径缓慢扩张至 8 mm 能够更加有效地缓解患者门静脉高压并发症,降低术后 HE 发生风险。本中心采用支架亚扩张策略 TIPS,也明显降低出血患者术后 HE 发生[11],临床医师应根据具体治疗目标选择支架尺寸。

2.3 门静脉压力梯度变化

Wan 等[12]研究显示 TIPS 术后门静脉压力降低越多,门体分流效果越明显,术后再出血风险也降低,但术后 HE 发生风险增高。TIPS 原理是建立从门静脉直接到体循环的通道,从而改善门静脉高压,同时也降低门静脉与腔静脉压力梯度,然而术后门静脉血流被大量分流到体循环,使得肝脏血供骤然下降,可引起肝功能不足,并增加术后 HE 发生风险[13]。此外,大量来自胃肠道含氨丰富的门静脉血流通过支架直接进入体循环,将引起机体血氨升高[6],而高血氨症是引发术后 HE 的重要诱因。因此,合理控制 TIPS 分流后门静脉压力梯度,个体化选择,可能是未来研究的一个方向。

3 影像学指标

3.1 脑血流和氧代谢

TIPS 术后患者脑血流量和氧代谢率下降[14],可作为发现术后早期脑功能障碍的指标。正电子发射断层成像(PET)和单光子发射计算机断层成像(SPECT)可检测支架植入前后脑血流量和氧代谢率变化,有利于观察到术后 HE 发生[15]。术后 HE 发生常伴随血氨升高,浓聚的氨干扰大脑正常能量代谢,引起脑血流量减少和氧供应不足,从而导致氧代谢率降低[14]。MR 动脉自旋标记(arterial spin abeling,ASL)成像也可观察到术后患者脑血流量减少[16]。此外,MR 波谱(magnetic resonance spectroscopy,MRS)成像可观察到术后发生 HE 患者颅内胆碱/肌酸和肌醇/肌酸下降[15],而胆碱和肌醇均为大脑能量来源,表明大脑能量代谢供应不足,脑功能障碍。TIPS 术后大脑能量代谢状态变化与 HE 发生的联系,可成为未来研究探索方向。

3.2 术前自发门体分流

患者术前检查发现的自发门体分流与术后并发症发生相关,尤其是术后早期 HE 发生[17]。术前进行门静脉 CTV 检查或多普勒超声检查可发现伴有自发门体分流,如胃食管分流、脾胃肾分流、脐静脉分流等患者,均与术后并发症发生风险上升相关[18]。因此,临床医师在抉择是否进行 TIPS 治疗时,可根据有无自发性门体分流的发生筛选出术后并发症发生风险较高患者,以制定更加合理的管理策

略。研究表明，对于孤立性胃底静脉曲张(isolated gastric varices,IGV)出血患者,可考虑在行 TIPS 治疗的同时联合应用球囊辅助顺行经静脉闭塞术(balloon-assisted antegrade transvenous obliteration, BAATO)封堵胃底曲张静脉和自发门体分流,能有效减少门静脉高压并发症如腹水、门静脉血栓[19]。

4　实验室指标

4.1　高血氨与低白蛋白

血氨浓度与术后 HE 发生关系密切，患者术后血氨越高发生 HE 风险越大[20]。TIPS 术后大量含氨丰富的血液直接进入体循环,机体血氨水平急剧升高,增多的氨通过血脑屏障进入大脑,破坏星形胶质细胞内谷氨酰胺代谢循环,导致大脑水肿,破坏正常神经递质功能，神经系统功能障碍致使 HE 发生[3]。此外,患者术前低白蛋白血症是术后发生 HE 的独立危险因素[7]。肝脏是人体内合成白蛋白的主要场所，术前低白蛋白血症表明肝脏合成功能差,且血清白蛋白水平低也与机体营养状况不良相关,而较差的肝功能和机体营养状况不良均会增加患者术后发生 HE 风险[21]。

4.2　低血钠与高血清肌酐

低血钠是术后 HE 发生的危险因素，并与术后 1 周内 OHE 发展关联密切[22-23]。肝功能失代偿期患者在发生低钠血症的同时常伴有高血氨症,将加剧大脑水肿,致使神经系统功能异常,增加 HE 发生风险[23-24]。失代偿期肝硬化患者由于血管加压素在肝脏灭活异常及门静脉高压形成，有效循环血量不足,常伴随稀释性低血钠[23];伴有难治性腹水患者大量应用利尿剂可致低血钠;个别患者发生静脉曲张大出血治疗时长期应用特利加压素,也会发生低钠血症[25]。此外,有研究证明患者术前高血清肌酐水平是影响 TIPS 术后 HE 发生的因素之一[17]。肾功能受损在肝硬化患者中十分常见,常预示着肝功能进一步失代偿[26],且有研究认为患者肾功能损伤与认知能力受损相关[27]。因此,临床医师在进行 TIPS 治疗前,应注意观察患者血钠和血清肌酐水平。

4.3　术后门静脉血高迁移率族蛋白 B1 水平变化

发生术后 HE 患者门静脉血高迁移率族蛋白(high mobility group protein,HMG)B1 水平显著高于未发生 HE 患者[28]。HMGB1 是一种晚期促炎因子，在急性肝损伤和慢性肝病患者血清中明显升高。HMGB1 改变可能与脑慢性神经炎症相关,将引起认知功能损伤[29]。此外,TIPS 治疗前后门静脉血 HMGB1 水平变化值越大,术后患者发生 HE 风险越高，表明术后门静脉 HMGB1 水平变化可作为预防术后 HE 的观察靶点[28]。

5　术前临床表现及术后管理

5.1　术前 CHE

患者术前若出现亚临床认知功能损伤即 CHE,则被认为是术后发生 OHE 的重要预测因素[30]。因此,TIPS 治疗前进行心理测试，筛选适合的手术患者,能有效降低术后发生 HE 风险[31]。但心理测试结果的准确性常取决于患者受教育程度或训练程度,因此需要量化标准对患者进行 CHE 排查。术前测定临界闪烁频率能直观地辨别精神心理活动异常患者,从而发现术前 CHE[32]。术前临界闪烁频率测定与术前心理测试相比易操作,可重复性高,结果更加客观。

5.2　骨骼肌减少症和营养不良

营养不良和骨骼肌减少症在肝硬化患者中的发生率为 23%～60%,多与患者不良预后密切相关[21]。肝脏是人体处理氨的主要场所,但肝硬化患者常伴有肝功能不全,此时骨骼肌便成为人体中氨代谢的主要场所[33]。若患者有骨骼肌减少症,机体排泄氨的能力下降,血氨水平随之上升。而术后早期饮食护理对改善患者营养状况和骨骼肌减少症具有积极意义[34],并有利于减轻机体处理氨的负荷,维持血氨水平[35]。Luo 等[34]研究报道 TIPS 术后患者经早期饮食干预后,HE 发病率由术前 28.3%降至术后 12.1%。临床医师在选择 TIPS 治疗时,应将骨骼肌减少症视为影响术后 HE 的预后因素，术前评估患者营养状况,术后及时进行饮食干预护理。

5.3　糖尿病

糖尿病患者经 TIPS 治疗后 HE 患病风险显著增加,可能与糖尿病引起的高血氨症和全身炎症有关[36-37]。主要由 3 个因素引起:谷氨酰胺酶活性增加,机体内产氨增多[38];胃肠道动力被抑制而引起便秘,致使肠道菌群失调和肠道细菌移位[39];糖尿病所致的全身慢性炎性反应[40]。谷氨酰胺在谷氨酰胺酶作用下水解为谷氨酸和氨,而 2 型糖尿病患者体内谷氨酰胺酶活性增高,机体产氨增多,血氨升高,大脑中谷氨酸积聚将引起星形胶质细胞水肿并破坏正常神经递质功能[36,38]。此外,糖尿病患者胃肠道蠕动频率低,便秘发生频繁,引起肠道内菌群生态失衡、肠道菌群移位,且其自身免疫力下降,因此抗感染能力下降,将增加机体感染风险,感染也是

术后发生 HE 的重要诱因[39]。再者，糖尿病患者处于慢性炎症状态，机体促炎因子释放增加，尤其是 2 型糖尿病患者体内可检测到肿瘤坏死因子(TNF)-α 和白细胞介素(IL)-6 增多，与 HE 严重程度密切相关[40]。

5.4 质子泵抑制剂(proton pump inhibitor，PPI)

PPI 应用可能增加 TIPS 治疗后患者发生 HE 风险，且随剂量增加而升高[41-42]。PPI 临床应用广泛，如胃炎、消化道溃疡的治疗等，但越来越多研究证据表明其应用与肝硬化门静脉高压并发症发生关系密切，尤其是 HE[43]。PPI 通过抑制胃肠道酸分泌提高肠道 pH，但其抑酸作用也会破坏胃酸屏障，引起肠道菌群生态失衡、菌群移位，导致自发性细菌性腹膜炎[44]，增加 TIPS 术后 HE 发生风险。据研究报道，TIPS 治疗后发生 HE 患者中应用 PPI 是未应用 PPI 者的 3 倍[41]；应用 PPI 并接受 TIPS 治疗患者中有 59.1%并无明确的 PPI 应用指征[42]。因此，临床医师要明确患者应用 PPI 指征，合理地选择进行 TIPS 治疗患者。

5.5 利福昔明

最新研究表明，利福昔明能有效预防 TIPS 术后一定时间内 OHE 发生[45]。利福昔明在治疗 HE 方面具优越性，并可有效降低肝硬化患者因 HE 发生的入院率[46]，常被用于肝硬化患者发生 HE 的二级预防[3]。Bureau 等[45]研究显示，通过 TIPS 术前 2 周和术后 6 个月给予患者利福昔明治疗，OHE 发生率降低 18%。因此，临床医师在 TIPS 术前后给予患者利福昔明，能有效降低术后 HE 发生。

6 综合预测模型

Child-Pugh 评分(CP 评分)在临床上广泛用于评价肝脏失代偿程度，CP 评分越高，患者肝功能越差。此外，由于门静脉高压，来自脾静脉的血液无法顺利回流至肝脏，因此蓄积的脾静脉血液可能造成肝病患者脾脏肿大，且回流的门静脉血量减少，肝脏血供也随之下降，而脾脏体积可在 CT 成像中定量测定。据此，本中心创新地提出 CP 评分联合 CT 测量脾脏体积，可客观定量地预测 TIPS 术后发生 HE 风险[47]，为临床预防 TIPS 术后 HE 提供新的参考依据。

终末期肝病模型(model for end-stage liver disease，MELD)评分系统采用量化指标，由血清肌酐、胆红素、国际标准化比值和病因组成，并构成死亡风险预测公式，常用于预测 TIPS 支架植入 3 个月后患者生存率[48]。Biggins 等[49]研究表明，血钠水平也是 TIPS 术后死亡的影响因素。于是 MELD 评分系统将患者术后血钠也包含进去，形成 MELD-Na 评分系统。

MELD-Na 评分系统以量化指标评估 TIPS 术后患者预后，但轻微 HE 在临床上常难以察觉，因此能否识别轻微 HE 成为患者术后 OHE 预后因素之一。HE 心理测试评分(psychometric hepatic encephalopathy score，PHES)可有效识别患者认知功能变化[30]，并检出轻微 HE，从而预防术后 OHE 发生。此外，血清白蛋白水平也与术后 HE 发生相关[13]，因此包含 PHES、术后血清白蛋白水平及术前 HE 发生的综合预测模型，可预判 TIPS 术后 HE 发生概率[30]，有利于临床预防和管理术后 HE。

7 结语

从 1971 年门体分流用于减小门静脉压力概念提出，1988 年 TIPS 治疗门静脉高压并发症得到广泛推广，到 1992 年我国完成首例 TIPS 手术[50]，经过 30 余年发展，TIPS 术硬件设施和技术理念日益完善，治疗门静脉高压及其并发症的效果日趋显著，术后分流功能障碍和 HE 等并发症风险逐渐降低[51-52]。但 TIPS 术后 HE 发生率仍较高，仍需为此进行大量深入研究。探究影响 TIPS 术后 HE 预后因素具有重要临床意义，有助于指导临床医师筛选 TIPS 术后 HE 高风险人群，予以早期预防，如加强饮食和药物干预，制定合理的管理方案，以降低 HE 发生风险，改善患者生存质量。寻找 TIPS 术后 HE 的合理预测指标，制定合适的风险分层标准，最终降低 TIPS 术后 HE 发生率，依然是目前需要重点关注的问题，值得进行更多探索。

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