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· 文献综述 ·

门静脉高压症行腹腔镜脾切除术后门静脉系统血栓形成 预测因子的研究进展

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摘要

腹腔镜脾切除术后门静脉系统血栓(PVST)形成具有高发生率、隐匿性与危害性。然而,腹腔镜脾切除术后PVST的最佳的诊断方式、治疗方案以及预测因子在国内外尚未形成统一意见。目前认为脾切除术后PVST发生的机制可能与血液高凝状态及血流动力学改变有关,其形成的原因大致为全身系统疾病和引起血流动力学变化的因素。全身性疾病包括恶性肿瘤、血液性疾病、自身免疫性疾病等,引起血流动力学变化的因素包括手术方式及时长、血浆D-二聚体、血小板计数、脾脏体积、脾脏最长直径、术前脾静脉直径及门静脉直径等。笔者对门静脉高压症行腹腔镜脾切除术后PVST形成预测因子的相关研究结果做一综述,旨在方便广大临床工作者对腹腔镜脾切除术后PVST形成进行风险评估,从而更加精准地把握抗凝时机,减少此并发症引起的严重后果,同时加快患者术后康复。

关键词

脾切除术, 腹腔镜; 门脉系统; 血栓形成 / 并发症; 危险因素; 综述

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Research progress of predictors for portal vein system thrombosis after laparoscopic splenectomy for portal hypertension

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Abstract

The formation of portal vein system thrombosis (PVST) after laparoscopic splenectomy has a high incidence, concealment and harmfulness. However, the optimal diagnosis, treatment plan and predictive factors for PVST formation after laparoscopic splenectomy have not yet reached an agreement either at home or abroad. At present, the mechanism for PVST after splenectomy may be related to blood hypercoagulability and hemodynamic changes, and the major causes for its formation are the systemic system diseases and the factors contributing to the hemodynamic changes. Systemic diseases include malignant tumors, hematological diseases, autoimmune diseases, etc. The factors causing hemodynamic changes include surgical methods and operation duration, plasma D-dimer, platelet count, spleen volume and its maximum diameter, preoperative splenic vein diameter and portal vein diameter. Here, the authors summarize the research results related to the predictors for PVST formation after laparoscopic splenectomy for portal hypertension, so as to provide convenience for clinicians to

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predict the formation of PVST after laparoscopic splenectomy, thereby to more accurately capture the timing of anticoagulation and reduce severe consequences of this condition, and meanwhile accelerate the postoperative recovery of the patients.

Key words

Splenectomy, Laparoscopic; Portal System; Thrombosis/comp; Risk Factors; Review

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门静脉系统血栓是指发生于门静脉系统的任何一段,包括门静脉主干及分支、脾静脉远端、肠系膜上静脉、肠系膜下静脉的血栓^[1]。据文献^[2]报道,开放的脾切除术和开放脾切除术联合贲门血管离断术后肝硬化患者的腹腔镜脾切术后门静脉系统血栓(portal vein system thrombosis, PVST)发生率分别为24%~29%和30%~48%。随着我国腔镜技术广泛应用,腹腔镜脾脏切除术成为肝硬化脾功能亢进患者的主流术式。而有研究^[3-5]表明,由于CO₂产生的气腹压力影响,患者的血流黏滞程度及动力学发生改变,腹腔镜脾切除术后PVST发生率更高。PVST发生较为隐匿,大部分患者血栓形成后常表现为无症状,由于治疗不及时,部分患者可导致严重的后果。从近期来看,不完全性门静脉系统血栓会使患者在术后出现持续性腹、胸水,延长住院时长;完全性门静脉系统血栓可以出现肠道缺血坏死,危及患者生命。从远期来看,门静脉主干血栓形成导致门静脉管壁硬化、管腔狭窄,使门静脉压力升高进一步加重消化道出血的风险^[6-8]。然而,脾切除术后PVST发生的具体机制仍在研究中,可能与血液高凝状态及血流动力学改变有关^[9-13]。本文对目前展现出较高临床价值的预测因子进行论述。

1 脾静脉直径及脾静脉直径手术前后差值

de'Angelis等^[14]收集了法国Henri Mondor医院进行腹腔镜脾切除术的170例患者资料。分析这些患者的影像学资料,并分别测量术前和术后在脾门连接处及距离它有2、4、6 cm的脾静脉直径。结果显示门静脉系统血栓形成患者的各处的术前脾静脉测量值均明显高于未形成患者。测量的各个部位的脾静脉直径 ≥ 8 mm的患者发生门静脉系统血栓的风险更高($OR=2.57$, $95\% CI=1.26\sim 5.23$, $P=0.009$)。通过对PVST亚组进行分析,发现大多数血栓形成涉及远端脾静脉(45.1%, 41/91),可能与术后脾静脉残端

血流动力学改变有关。41.7%的患者在多个部位有血栓形成。单个部位形成血栓预示良好的预后($P<0.000 1$)。然而,在各测量部位的PVST和无PVST组之间,术前和术后平均脾静脉直径的下降值无显著差异。在4个测量位置和PVST以及非PVST组中,脾静脉直径的下降值也在较大的脾静脉直径(≥ 8 mm)和较小的脾静脉直径(≤ 8 mm)之间进行比较,无显著差异。这与Danno等^[15]报道恰恰相反,他们在PVST组比非PVST组中观察到更大的脾静脉直径降低,所以他们推测更高的脾静脉直径减少率与更高的PVST发生率相关。同时,在一项单中心回顾性分析中,Kuroki等^[16]在增强CT上测量腹主动脉左边缘水平的脾静脉直径(腹主动脉左边缘的水平被认为是一个突出的解剖标志)。为了确定脾静脉直径的准确截断值以用作PVST形成的预测因素,进行了接收者工作特征曲线(ROC)分析显示,ROC曲线下的面积(AUC)为0.937(95% CI=0.873~1.000),计算出的最佳截断值为10 mm。由上述研究表明,术前脾静脉直径大小是一个有价值的预测因子,而手术前后脾静脉直径差值是否可对PVST形成预测,仍需要更多临床研究证据。

2 早期使用抗凝及抗血小板药物

迄今为止,尚无标准的公认抗凝方案可预防脾切除术后患者的PVST形成^[17]。最常见的抗凝方案是在围手术期使用抗凝药(低分子肝素、口服华法林)或抗血小板药物(阿司匹林,氯吡格雷硫酸氢盐和双嘧达莫)^[18-20]。Jiang等^[2]进行了针对75例腹腔镜脾切除术后患者连续3个月随访的回顾性队列研究。多元逻辑回归分析显示:华法林治疗是术后30 d和90 d PVST形成的独立阳性预测指标,而术后第7天并未观察显著性差异。在这项研究中,术前国际标准化比值(international normalized ratio, INR)是术后90 d时PVST的独立阳性预测指标。术前INR升高的患者术后INR也

升高,这可能有助于降低PVST的发生率。但是,INR并不是术后7 d和术后30 d上PVST形成的独立阳性预测指标,可能是华法林延长INR的能力可能在其改善PVST发生率中起了重要作用,而早期阶段使用华法林并不能有效地阻止术后PVST的形成。相比之下,术后血液动力学变化和血小板计数急剧增加脾切除可能促进了PVST的形成。由此研究可以推测,华法林在PVST形成的急性期可能具有较少的活性,但连续治疗可能会增强其治疗活性。王泉雄等^[21]收集武汉大学中南医院130例行腹腔镜脾切除术患者资料,根据患者资料自愿选择是否使用抗凝药,分为抗凝组(73例)和非抗凝组(57例)。观察抗凝组与非抗凝组对术后PVST形成的临床疗效。多因素Logistic回归分析结果表明,抗凝药物使用是PVST的一个独立的保护因素($P=0.001$)。许桐林等^[22]研究对脾切术后早期应用低分子肝素加阿司匹林,结果显示抗凝组有更低的PVST发生率。综上研究结果可得出结论:围手术期应用抗凝治疗可降低术后PVST的发生率,是PVST形成的预测因子。

3 门静脉系统血流动力学改变

Kawanaka等^[23]研究腹腔镜脾切术后门静脉系统血流动力学改变的试验中,发现18例腹腔镜脾切除患者中测量的肝静脉压梯度在脾切除后降低了25%,门脉血管阻力也降低了21%。在肝硬化门静脉高压症患者中,脾切除术后使内脏血流减少,以及通过使内皮素-1(ET-1)和NO代谢物(NO_x)的肝浓度正常化来减少肝内血管阻力。尉鹏等^[24]回顾性分析72例接受腹腔镜脾切除治疗的门脉高压继发脾亢患者临床资料,结果显示门静脉直径以及手术前后门静脉血流速度差值为术后并发PVST的危险因素($P<0.05$)。手术前后门静脉血流速度差值、门静脉直径分别为4.06 cm/s、12.89 mm时对PVST具有较好的预测价值。腹腔镜脾切除术后对患者门静脉血流动力学改变程度可能对PVST形成具有潜在的预测价值。

4 术后血小板计数

Szasz等^[25]对520例脾切除术患者资料进行分析进行了回顾性分析,其中344例以开腹方式完成,176例完全腹腔镜完成。PVST的总发生率是

为6.7%(35/520),开腹为6.1%(21/344),腹腔镜入路为8.0%(14/176)。ROC曲线显示血小板计数是PVST发生的良好预测指标,所有脾切除患者的AUC为0.77(95% CI=0.69~0.86, $P<0.001$),以开放方式完成的患者为0.7(95% CI=0.59~0.81, $P<0.001$),以腹腔镜完成的患者为0.88(95% CI=0.77~0.99, $P<0.001$)。对于腹腔镜队列最佳截断值为 $659 \times 10^9/L$ 。这些血小板计数的诊断准确度为61%~86%,阴性预测值(NPV)为97%~99%。脾切除术后血小板计数常呈现反跳性增高,可能由于血流黏滞程度上升而导致PVST形成,故可将术后血小板计数作为PVST形成的预测因子^[26-28]。

5 术后D-二聚体

李大伟^[29]选择47例因肝炎后肝硬化门脉高压症行腹腔镜脾切除术患者,测定患者术前与术后1、7、14 d的血浆D-二聚体水平,并对D-二聚体水平的术后PVST形成诊断效能行ROC分析。PVST组与非PVST组患者脾切除术后血浆D-二聚体水平持续升高,但PVST组术后7、14 d的D-二聚体水平明显高于非PVST组($P<0.05$)。术后7 d血浆D-二聚体水平对脾切术后PVST诊断准确性的ROC的AUC为0.780($P<0.05$)术后血浆D-二聚体持续较高水平(≥ 14 mg/L)者,发生PVST的危险性较大。尉鹏等^[24]也认为术后血浆D-二聚体可作为PVST的预测指标,并绘制ROC曲线确定最佳截断值为12.96 mg/L。D-二聚体是交联纤维蛋白经纤溶酶作用后所形成的终产物之一,在临床中主要是用于对机体高凝状态或者纤溶亢进进行评估的标志物^[30-33],故可考虑将其作为PVST形成的预测因子。

6 手术时间

不同的手术方式PVST发生率不同,由于气腹压力影响,腔镜手术可能存在着更显著差异(如单纯的腔镜脾切除术与腔镜脾切联合贲门血管离断术)。而即使相同的手术方式,因术者对腔镜技术的熟练程度及病人情况不同,所用时间也不同。Kuroki等^[16]研究显示,PVST组的手术时间明显长于非PVST组(中位时间:238 min vs. 190.5 min, $P=0.012$),提示手术时间可对PVST形成进行预测。

7 脾脏重量

Kuroki等^[16]单个中心研究结果显示, PVST组的中位脾脏重量显著大于非PVST组(547.5 g vs. 253.5 g, $P < 0.001$), 同时我们在Kawanaka等^[23]研究中发现, 门静脉的血流量、门静脉截面积和门静脉充血指数与脾脏大小有关($P < 0.05$), 故可推测脾脏重量大小间接引起门静脉血流动力学改变而促进PVST形成, 脾脏重量是PVST形成间接预测因子。

腹腔镜脾切除术不仅有创伤小, 恢复快等诸多优点, 尤其对肝功能分级Child-Pugh B的患者的肝功能有所改善^[33-36]。但是腹腔镜脾切除相关PVST形成风险可能升高, 如何积极预防是临床工作者的关键问题, 故而探索PVST形成的预测因子具有重大意义。大部分综述是针对开腹的脾切除术后PVST形成的预测因子及危险因素进行归纳, 而腹腔镜由于气腹部压影响, 手术方式及时间的不同, 导致术后PVST形成的预测因子存在一定差异^[37-39], 故而对上述预测因子进行总结。少数临床研究也表明其他因素在PVST组与非PVST组存在差异, 如术前血小板计数、凝血功能、体质量指数、脾脏最长直径等, 这些因素可能由于研究样本少量, 实验方案异质性, 导致产生统计差异的偶然性, 并不能作为可靠的预测因子。若要提高它们的证据等级, 则需要有更多试验研究特别是随机对照试验支持。全身疾病因素可能是PVST形成的危险因素, 如恶性肿瘤、血液疾病及免疫性疾病患者, 它们可能通过释放细胞因子、抗体补体影响血液的黏滞度^[40], 而此综述主要是对因肝硬化行腹腔镜脾切除患者术后PVST形成预测因子进行讨论, 排除了全身疾病因素的影响, 故上述预测因素有其特异性。为了更精确预测腹腔镜手术后PVST形成, 实现更精准的抗凝治疗, 仍需要更多临床研究数据支持。

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