

下肢深静脉血栓形成后综合征危险因素及预防策略的研究进展

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摘要

下肢深静脉血栓形成后综合征(post-thrombotic syndrome, PTS)是深静脉血栓形成(deep vein thrombosis, DVT)最常见的慢性并发症, 可造成患者生活质量的严重下降。目前, 早期识别PTS的高危患者并加以干预仍是临床关注的重点, 但PTS相关的危险因素以及预防策略的实施细节仍有争议。本文对PTS的危险因素和预防策略进行了综述, 以期为PTS预防体系构建提供借鉴, 降低PTS发生率。

关键词

血栓形成后综合征, 下肢深静脉血栓形成, 危险因素, 预防策略

Research Progress on Risk Factors and Preventive Strategies of Lower Extremity Post-Thrombotic Syndrome

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Abstract

Lower extremity post-thrombotic syndrome (PTS) is the most common chronic complication of deep vein thrombosis (DVT), which can cause serious decline in patients' quality of life. At present, early identification of patients at high risk of PTS and intervention remain the focus of clinical at-

tention, but the risk factors for PTS and the implementation details of preventive strategies are still controversial. This article reviewed the risk factors and preventive strategies of PTS, in order to provide reference for the construction of PTS prevention system and reduce the incidence of PTS.

Keywords

Post-Thrombotic Syndrome, Deep Vein Thrombosis, Risk Factors, Preventive Strategies

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1. 引言

血栓形成后综合征(post-thrombotic syndrome, PTS)是下肢深静脉血栓形成(Deep Venous Thrombosis, DVT)后,由于静脉阻塞和深静脉瓣膜受损,导致长期的下肢静脉高压和血液回流障碍所引起的腿部疼痛、沉重、肿胀、瘙痒、色素沉着、浅静脉扩张以及静脉溃疡等一系列综合症。PTS 作为一种长期慢性的血管疾病,即便在 DVT 后进行有效的抗凝治疗,也可影响 30%~50%的患者[1]。据报道,PTS 对患者生活质量上的影响已经超过了糖尿病[2]。此外,重度 PTS 导致的一系列临床症状显著增加了 DVT 后医疗保健的花费,加重了患者的经济负担[3]。鉴于我国人口老龄化和血栓性疾病负担加重,PTS 的社会影响将会持续增加。

随着血管腔内治疗技术的不断发展,髂股静脉病变的腔内支架置入术已成为中重度 PTS 的临床一线治疗,但支架内血栓形成或慢性闭塞的再干预率仍较高。据报道,尽管同时进行抗凝治疗,PTS 腔内支架置入术后 6 个月随访有 13.7%的患者发生并发症[4]。因此,在 DVT 发生后,准确识别 PTS 的高危患者并施行预防策略尤为重要。目前关于 PTS 的危险因素和预防策略实施的细节仍有争议,本文基于国内外有关 PTS 的临床证据,对 PTS 的危险因素和预防策略进行综述,重点关注 PTS 发生相关的生物标志物,以期降低 PTS 发生率。

2. PTS 的危险因素

目前国内外文献关于 PTS 危险因素的分类存在较多差异,包括可控因素和不可控因素、患者特异性因素和 DVT 相关因素以及 DVT 诊断时的危险因素和随访中的危险因素。其中,性别、诱发性或无诱因的 DVT 以及遗传性血栓形成倾向已被证明与 PTS 发生风险无关或影响较小[5] [6]。基于 PTS 长期慢性疾病的特点,为优化患者院内外的全程管理,现根据 DVT 患者诊断及随访的时间点差异对 PTS 危险因素进行综述。

2.1. DVT 诊断时的危险因素

2.1.1. 高龄

高龄早已被确定为是 PTS 的独立危险因素[5]。据报道,高龄 DVT 患者发生 PTS 的风险可增加 3 倍 [7]。刘锋等[8]人的研究还显示了年龄(≥ 60 岁)是近段 DVT 后发生重度 PTS 的独立危险因素,其潜在机制可能与老年人静脉血管的老化、血液粘度增高,静脉瓣膜功能减退相关。

2.1.2. DVT 的性质(近段、症状性、非急性期)

PTS 的发生与 DVT 位置密切相关,近段 DVT (尤其血栓累及髂股静脉)使 PTS 风险增加 2~3 倍[9] [10]。Stain 和 Cowel 等人的研究也显示相较于远段 DVT,近段 DVT 患者发生 PTS 的风险更高[11] [12]。此外,多项研究表明 DVT 诊断时的严重症状对于 PTS 的发生具有预测作用[13] [14]。黄天安等[15]研究还发现非急性期的 DVT (病程超过 2 周)是 PTS 的独立危险因素。与孤立性的远段血栓相比,近段 DVT 通常伴随着更严重的症状,血栓溶解的时间也更长。随着病程的延长,血栓对于血管壁的炎性刺激以及瓣膜功能的损伤均更严重,导致血管的纤维闭塞和不可逆的瓣膜损伤,最终形成静脉高压而产生 PTS。

2.1.3. 下肢静脉曲张

DVT 前已发生的下肢静脉曲张会独立增加 PTS 的风险[8] [15]。下肢静脉曲张属于慢性静脉功能不全疾病,也可能表现为沉重、肿胀、色素沉着、浅静脉扩张甚至溃疡等症状。在临床表现上,下肢静脉曲张与 PTS 具有协同效应,使患者评估 PTS 的 Villalta 评分明显升高。两者在病理生理上均为静脉高压改变,原发性下肢静脉曲张是浅静脉瓣膜关闭不全,血液返流导致的,而 PTS 是因为 DVT 后深静脉慢性闭塞、瓣膜功能损伤。

2.1.4. 肥胖和超重

肥胖,即体重指数(Body Mass Index, BMI)大于 30 kg/m^2 会使 PTS 的风险增加近 2 倍[7]。肥胖患者因为炎症介质增加和纤溶活性下降,血液粘稠处于高凝状态,不利于血栓的溶解。同时,肥胖患者的腹腔压力相对较高,下肢肌肉泵的力量较弱,进一步削弱了静脉回流能力,最终形成静脉高压导致 PTS 的发生。近期国内有研究表明,超重(BMI $> 24 \text{ kg/m}^2$)也是 DVT 后 PTS 发生的独立预测危险因素[16]。Kahn 等[9]的研究还显示, BMI 每增加 1 kg/m^2 , PTS 的 Villalta 评分增加 0.14 分。

2.1.5. 其他合并症

少数研究显示,糖尿病、慢性肾病、恶性肿瘤以及吸烟史可能是 PTS 的危险因素[17] [18] [19],但缺乏普遍性,仍需要更多大型临床研究支持。

2.2. DVT 随访时的危险因素

2.2.1. 残余静脉梗阻

根据 Agrawal 等[20]学者的定义,残余静脉梗阻指 DVT 初始抗凝治疗结束后仍存在占管腔直径至少 40% 的血栓。多项国内外研究已表明残余静脉梗阻是 PTS 发生的危险因素[21] [22] [23]。近期荷兰一项长达 5 年的前瞻性队列研究报道,存在 RVO 的患者 PTS 的发生风险是普通患者的 1.66 倍[24]。残余静脉梗阻表明静脉血管的纤维性狭窄甚至闭塞,不利于血液回流,容易形成了下肢静脉高压,导致 PTS 的发生。此外,一些研究显示, DVT 后持续存在的下腔静脉滤器会一定程度影响血液回流,增加下腔静脉血栓形成、梗阻的风险, PTS 的发生率也会增加[8] [25]。

2.2.2. 深静脉返流

在 DVT 治疗后随访期间,影像学检查发现深静脉的瓣膜返流会显著增加 PTS 的风险[22]。目前,对 PTS 的评估通常在 DVT 发生后 6 个月进行,最少也是 3 个月[2] [22]。在这之前出现的深静脉返流,往往伴随着更严重的慢性静脉功能不全症状,预示着患者更高的 PTS 风险。

2.2.3. 抗凝不顺应性

根据欧洲血管外科学会 2021 年静脉血栓形成指南,抗凝不顺应性定义为诱发性 DVT 患者接受抗凝治疗少于 3 个月、无诱因 DVT 患者抗凝治疗少于 6 个月、抗凝期间不规律用药以及接受华法林抗凝的患

者国际标准化比值(International Normalized Ratio, INR)低于治疗范围(2~3)至少 2 次。DVT 后进行规律有效的抗凝治疗可以减少 PTS 的风险已得到广泛的证实[26] [27]。Chitsike 等人[28]进行了一项多中心队列研究发现, 接受华法林抗凝治疗的 DVT 患者, INR 多次低于治疗范围发生 PTS 的风险将升高近 1 倍。

2.2.4. DVT 的复发

DVT 的复发被视为 PTS 的独立危险因素,特别是同侧 DVT 复发,可使 PTS 的风险增加 3 倍以上[29]。此外, RIETE 登记处的研究还进一步证实复发性的 DVT 是重度 PTS 的危险因素[19]。复发的血栓会加重了对血管壁和静脉瓣膜的损伤, 更容易引起静脉慢性闭塞和血液返流。总之, 预防 DVT 复发就是预防 PTS 发生的最重要手段。

2.2.5. 生物标志物

近年来, 有关 PTS 生物标志物的研究越来越多。炎症因子和纤溶系统的相互作用在 PTS 发病机制中占据重要地位。C 反应蛋白(C-reactive protein, CRP)作为最常见的炎症指标之一, 研究显示 DVT 后 CRP 的水平持续升高与 PTS 的发生显著相关[30]。此外, 中性粒细胞/淋巴细胞的比值升高是 PTS 的独立危险因素[31]。一项涉及 320 名 DVT 患者的前瞻性的研究还显示, DVT 后 3 个月测量的脂联素和瘦素水平可预测 PTS 的发生[32]。多项研究表明, 黏附分子 ICAM-1 显示出了与 PTS 发生的相关性[33] [34]。其他细胞因子包括 IL-6、IL-8、IL-10、TNF- α 等与 PTS 发生的关系则显示出不一致的结果, 还需进一步研究[34]。基质金属蛋白酶(matrix metalloproteinase, MMP)是一组参与细胞外基质重塑的蛋白水解酶, 在血栓后纤维化形成中发挥着重要作用。Francisci 等[35]人的研究显示 MMP-1 和 MMP-8 水平升高和较高的 PTS 风险相关。

Rabinovich 等[36]人研究显示 D-二聚体和纤维蛋白稳定因子与 PTS 发生显著相关。多项研究表明了纤溶系统的标志物与 PTS 之间潜在的联系, 但存在一定的异质性[32] [37] [38]。目前仍需要更多的前瞻性研究来阐明这些标志物是否真实有助于预测 PTS 的发展。

3. PTS 的预防策略

现阶段, PTS 的预防主要基于 DVT 的规范治疗, 压力治疗、运动锻炼和生活方式改善也有助于降低 PTS 的发生率。

3.1. 标准的抗凝治疗

标准的抗凝治疗仍是预防 PTS 最有效的策略, 其通过防止血栓扩散来达到早期溶解血栓, 并降低血栓复发的概率, 从而减少瓣膜损伤和残余静脉阻塞的可能。在抗凝药物的选择上, 研究显示, 使用新型口服抗凝药后的 PTS 发生率较使用华法林降低, 原因可能是新型口服抗凝药无需测定 INR, 抗凝效果更稳定[27]。另有研究表明, 低分子肝素由于其稳定的抗凝作用以及潜在的抗炎效果, 在预防 PTS 和静脉溃疡上, 要优于华法林甚至新型口服抗凝药[39]。此外, 关于抗凝时长, 一项随机对照试验证明, 延长抗凝治疗的时长对于改善 PTS 临床结果没有明显益处[40]。

3.2. 早期血栓清除

随着对血栓认识的不断深入和腔内治疗技术的持续发展, 早期清除血栓(导管接触性溶栓、经皮机械性血栓清除术等)在降低 PTS 的发生率和严重程度上的作用越发受到重视。多项随机对照试验发现, 早期血栓清除策略在预防 PTS 以及重度 PTS 方面比单独抗凝更有效[41] [42] [43]。对于急性、近段深静脉血栓的患者, 早期血栓清除策略有助于尽快恢复静脉血流, 保护血管内皮, 恢复瓣膜功能, 减少残余血栓的可能性, 最终降低 PTS 的风险。而这种益处伴随着大出血风险的增加[44], 需要临床医生严格控制早

期血栓清除策略的指征。国内也有研究显示,对于合并髂静脉狭窄的 DVT 患者,髂静脉的腔内成形术也可降低 PTS 发生风险[15]。

3.3. 其他药物预防

舒洛地特是一种口服的糖胺聚糖混合物,具有抗血栓、抗炎和内皮保护作用,对于预防 PTS 和静脉曲张也有一定的效果[45]。有研究显示,他汀类降脂药物对与预防 PTS 具有潜在的保护作用,但尚缺乏随机对照试验证据[46]。尽管地奥司明、七叶皂苷等静脉活性药物可有效缓解慢性静脉功能不全的症状,在预防 PTS 的证据上依旧不足[47]。

3.4. 压力治疗

压力治疗仍是大部分 PTS 的主要治疗方法。梯度压力袜(Graduated compression stockings, GCS)对于 PTS 的预防作用也早已被证实,但由于研究之间存在相当较大异质性,现有的证据级别较低[48] [49]。中高压(30~50 mmHg)和长筒型的 GCS 带来的穿戴困难以及不适感,使得使用者的依从性明显降低。部分随机对照试验显示[50] [51], GCS 的长度(中筒或长筒)、压力梯度(低压力或中高压)以及使用时间(1 年或 2 年),对于 PTS 的预防作用并没有明显差异,甚至并不能降低 PTS 的风险。目前, GCS 在 PTS 预防方面的有效性以及应用细节仍有待进一步的探索。

3.5. 运动锻炼和生活方式的改变

运动锻炼能够增强下肢的肌肉泵功能,有利于下肢静脉的血液回流,一定程度上改善患肢的肿胀,减轻 PTS 的症状。现阶段,运动锻炼对预防 PTS 的作用尚缺乏可靠的临床证据,但至少不会导致 PTS 症状的恶化[52]。肥胖患者减重可降低中心静脉压来一定程度上改善 PTS 症状,但目前仍没有高质量的证据证明减重可降低 PTS 的发病风险。吸烟是众多心血管的危险因素,对 DVT 患者来说,戒烟、减重等健康的生活方式在预防 PTS 上至少是无害的。

4. 小结

PTS 仍是 DVT 后最常见、最严重的长期并发症之一。在 DVT 的诊治和随访期间,早期识别 PTS 高危患者,并实施有效的预防策略具有明显的益处。除对 DVT 进行系统的抗凝和血栓清除外,药物预防、压力治疗、运动锻炼以及生活方式的改变也是 PTS 预防的重要组成部分。炎症因子和纤溶系统相关的生物标志物在预测 PTS 发生中展现了可观的价值,在未来的 PTS 预防体系构建中应考虑使用这些生物标志物,以帮助对 PTS 高风险患者实施更积极的预防策略。

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