

doi: 10.13241/j.cnki.pmb.2019.18.042

经皮导管接触溶栓腔内治疗与标准抗凝治疗用于急性下肢深静脉血栓的临床效果比较*

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摘要 目的:分析和比较经皮导管接触溶栓腔内治疗与单纯标准抗凝治疗急性下肢深静脉血栓形成的临床效果的安全性。**方法:**回顾性分析 93 例中央型(髂股静脉)和混合型(全下肢深静脉)深静脉血栓患者临床资料,根据治疗方法的不同分为导管溶栓治疗组(试验组)65 例、单纯抗凝治疗组(对照组)28 例,比较两组患者治疗后患肢消肿率、下肢深静脉血栓的溶栓率及并发症的发生率。**结果:**治疗后,试验组患者患肢大腿消肿率 $[(83.03 \pm 4.53) \%$]显著高于对照组 $[(50.42 \pm 7.41) \%$]($P < 0.05$);患肢小腿消肿率 $[(76.48 \pm 8.24) \%$]亦显著高于对照组 $[(54.95 \pm 8.14) \%$]($P < 0.05$)。试验组患者下肢深静脉血栓溶栓有效率为 92.31%(60/65),显著高于对照组 $[14.29 \%(4/28)]$ ($P < 0.05$)。随访半年后,试验组患者下肢血管的通畅率为 90.67%(57/65),PTS 率为 7.69%(5/65);而对照组患者下肢血管的通畅率为 21.42%(6/28),PTS 率为 14.28%(4/28)。试验组血管通畅率明显高于对照组($P < 0.05$),而 PTS 发生率明显低于对照组($P < 0.05$)。两组患者并发症发生率比较差异无明显统计学意义($P > 0.05$)。**结论:**经皮导管接触溶栓腔内治疗急性中央型和混合型下肢深静脉血栓的短期疗效优于单纯抗凝治疗,且两种方法的安全性相当。

关键词:急性下肢深静脉血栓形成;导管溶栓;腔内治疗

中图分类号:R654.3;R543 文献标识码:A 文章编号:1673-6273(2019)18-3589-05

Comparison of the Therapeutic Effects of Catheter-directed Thrombolysis and Standard Anticoagulation for the Lower Extremity Deep Vein Thrombosis*

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ABSTRACT Objective: To analyze and compare the clinical effect and security of catheter-directed thrombolysis (CDT) and standard anticoagulation in the treatment of acute deep venous thrombosis (DVT). **Methods:** The clinical data of 93 cases of acute central type DVT (iliofemoral) and Entire Limb DVT inpatients were retrospectively analyzed. According to the treatment, the patients were divided into 65 cases of catheter-directed thrombolysis group (trial group) and 28 cases of standard anticoagulation treatment group (control group). The limb swelling remission rate, deep vein thrombolysis rate and complication rate were compared between the two groups. **Results:** For the central type DVT and the entire limb DVT, the thigh swelling remission rate of trial group had $(83.03 \pm 4.53) \%$ was significantly higher than that of the control group $(50.42 \pm 7.41) \%$; and the calf swelling remission rate of trial group was $(76.48 \pm 8.24) \%$, which was also significantly higher than that of the control group $(54.95 \pm 8.14) \%$, ($P < 0.05$). For the central type DVT and the entire limb DVT, the thrombolysis rate of deep vein in the trial group was 92.31% (60/65), which was significantly higher than that of the control group $[14.29 \%(4/28)]$ ($P < 0.05$). After half a year of follow-up, the patency rate of trial group was 90.67% (57/65), and the incidence of PTS was 7.69% (5/65), but the patency rate of control group was 21.42% (6/28), the incidence of PTS was 14.28% (4/28). The complications rate of the two groups showed no obvious statistical difference. **Conclusion:** The short-term clinical effect of catheter-directed thrombolysis treatment for the acute central type DVT (iliofemoral) and the entire limb DVT is better than that of standard Anticoagulation and the security of catheter-directed thrombolysis (CDT) is equal to that of standard anticoagulation treatment.

Key words: Acute deep vein thrombosis; Catheter-directed thrombolysis; Endovascular treatment

Chinese Library Classification(CLC): R654.4; R543 **Document code:** A

Article ID: 1673-6273(2019)18-3589-05

前言

下肢深静脉血栓形成(deep vein thrombosis, DVT)是一种

常见的外周血管疾病^[1,2],急性下肢深静脉血栓脱落可致肺栓塞(pulmonary embolism, PE);血栓机化、血管结构和瓣膜的破坏导致后期多数患者出现不同程度的血栓形成后遗症

* 基金项目:国家自然科学基金项目(81601621)

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(收稿日期:2018-12-28 接受日期:2019-01-25)

(post-thrombotic syndrome, PTS)^[3,4]。急性 DVT 的治疗目的是尽快减轻患者下肢肿胀、疼痛的临床症状,降低 PE 和 PTS 的发生率^[5,6]。单纯的标准抗凝能抑制血栓蔓延,降低肺栓塞的发生率,预防血栓复发,但不能有效加速溶栓^[7,8],2 年后仍有 20-55 % 的 DVT 患者将发展为 PTS^[9]。

而经皮接触性导管溶栓(CDT)与系统溶栓相比具有更少的出血并发症和更高的血栓溶通效率^[10,11]。本文拟通过回顾分析 2015 年 1 月至 2018 年 3 月在亳州市人民医院诊治的 93 例中央型和混合型 DVT 患者的临床资料,分析 CDT 腔内治疗联合抗凝治疗与单纯抗凝的治疗效果。

1 资料和方法

1.1 患者入组资料

选择 2015 年 1 月至 2018 年 3 月期间亳州市人民医院血

管外科收治的 DVT 患者。纳入临床研究的标准:① 有典型的 DVT 临床表现:下肢肿胀、疼痛或压痛等。② 病程小于 2 周。③ 多普勒彩超或静脉造影证实为中央型(髂股静脉)或混合型(全下肢深静脉)DVT。排除标准:① 病程大于两周的 DVT 患者。② 血栓未累及髂股静脉患者。③ 存在抗凝和溶栓治疗禁忌的患者。所有纳入研究的患者,均建议其行 CDT 治疗,患者权衡各方面利弊后最终选择治疗方式。本研究共纳入男性患者 36 例,女性患者 57 例,平均年龄 53.41 ± 7.36 岁(29-71 岁),左下肢 DVT 患者 56 例,右下肢 DVT 患者 34 例,平均发病时间 5.42 ± 3.66 天。其中,选择行 CDT 治疗患者 65 例(试验组),单纯抗凝患者 28 例(对照组)。两组患者年龄、性别、发病时间、DVT 分型和治疗前后患肢大、小腿周径差(患肢大腿周径分别为距髌骨上缘 10 cm、小腿周径为小腿最粗处)等相关指标相比较均无统计学差异($P > 0.05$, 表 1)。

表 1 两组患者入院基本情况比较
Table 1 Comparison of the basic information between the two groups

Groups	Age	Gender		time (day)	Types of DVT	
		Male	Female		central	mixed
Trial group (n=65)	53.38 ± 14.31	25	40	5.18 ± 3.85	30	35
Control group (n=28)	53.43 ± 14.82	11	17	5.89 ± 3.64	12	16
P value	$P > 0.05$	$P > 0.05$		$P > 0.05$	$P > 0.05$	

Note: Values of $P < 0.05$ denoted statistical significance.

1.2 方法

1.2.1 试验组 所有纳入研究患者入院均立即卧床、患肢制动、抬高患肢,予以低分子肝素皮下注射,用量约为 100 U/ 每公斤体重, q12 h 应用;所有行 CDT 患者均经健侧股静脉穿刺造影,若血栓累及下腔静脉,则行右侧颈静脉穿刺下腔静脉造影,明确双肾静脉开口位置,于肾静脉下方 0.5-1 cm 处植入可回收下腔静脉滤器,根据治疗情况并于 2-4 周后取出滤器。

中央型 DVT 患者多选择在多普勒彩超引导或 DSA 路途引导下经腘静脉穿刺入路,混合型 DVT 患者多选择在多普勒彩超引导或 DSA 路途引导下经小隐静脉、胫前静脉或胫后静脉穿刺入路,将 Unifuse 溶栓导管插入静脉血栓中,导管头端定位于血栓近端,植管成功后推注 12.5-25 万单位溶栓药物(尿激酶),后持续以 40-100 万单位 / 天的尿激酶剂量自溶栓导管泵入,每天监测凝血功能,根据纤维蛋白原(Fg)的结果调节尿激酶用量,当 Fg 小于 1.5 g/L 时减少尿激酶用量,小于 1.0 g/L 时停用尿激酶,溶栓 3-4 日经导管造影检查血栓溶解情况,血栓完全溶解或血栓溶解无进展时终止溶栓,溶栓时间一般不超过 7 天。溶栓成功后造影发现髂静脉残余狭窄在 50%以上者,告知患者病情,建议同期行球囊扩张支架植入术(图 1)。术后给予华法林或利伐沙班抗凝 6 个月,口服华法林患者定期监测凝血功能,控制国际标准化比值在 2-3 间;口服利伐沙班剂量为 15 mg bid(前 3 周),3 周后改为 10 mg bid。

1.2.2 对照组 所有纳入研究患者入院均立即卧床、患肢制动、抬高患肢 2 周,予以低分子肝素皮下注射,用量约为 100 U/

每公斤体重, q12 h 应用,在应用低分子肝素后 3-5 天后加用华法林,起始量为 2.5 mg/ 天,定期复查凝血功能,根据国际标准化(INR)调整华法林用量或口服利伐沙班剂量为 15 mg bid(前 3 周),3 周后改为 10 mg bid,抗凝 6 月。定期复查下肢血管多普勒彩超评估血栓治疗情况,口服华法林期间控制 INR 在 2-3 之间,并长期穿弹力袜。

1.3 疗效评价

比较两组患者治疗后患肢消肿率、深静脉溶栓率及并发症的发生率。消肿率通过比较治疗前后健、患侧大腿膝关节上 10 cm 处和小腿最粗处的周径差。血栓溶解分级为:Ⅲ级为 100%血栓完全溶解,无残留;Ⅱ级为 50~99 % 的血栓溶解;Ⅰ级为小于 50%的血栓溶解;Ⅲ级和Ⅱ级表示溶栓有效。不良反应包括两组患者在住院治疗期间出血、肺栓塞、血栓进展的发生情况。

1.4 随访

术后 1 月、3 月和 6 月门诊复查多普勒超声或顺行静脉造影以评估下肢静脉通畅情况,并记录半年后两组患者 PTS 的发生率。

1.5 统计学分析

所有数据应用 SPSS 17.0 统计软件进行统计分析。计量资料以均数 $\pm$ 标准差表示($\bar{x} \pm s$),两组间数据比较采用 t 检验;非正态分布的计量资料两组间比较用非参数 Kruskal-Wallis H 检验;计数资料两组间比较用 χ^2 检验。 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 两组患者治疗前后患肢与健肢周径差及患肢消肿率比较 (表 2、表 3)

两组患者治疗后 3 天、7 天及 2 周时患肢与健侧肢体周径

差较治疗前明显减小,且试验组患者治疗后各时间点患肢与健侧肢体周径均差明显小于对照组, ($P<0.05$)。试验组患者治疗 2 周后患肢大腿消肿率 $[(83.03\pm 4.53)\%]$ 显著高于对照组 $[(50.42\pm 7.41)\%]$ ($P<0.05$);患肢小腿消肿率 $[(76.48\pm 8.24)\%]$ 显著高于对照组 $[(50.42\pm 7.41)\%]$ ($P<0.05$)。

表 2 两组患者治疗前后患肢与健侧肢体大腿膝上 10 cm 处周径差及消肿率
Table 2 The thigh swelling remission rate were evaluated between the two groups after treatment

Groups	Differentials of the thigh circumference (mm)				Rate of the thigh swelling remission%
	Before treatment	At 3 days after treatment	At 7 days after treatment	At 2 weeks after treatment	
Trial group(n=65)	57.28± 10.15	28.50± 11.81	15.46± 10.37	9.72± 9.78	83.03± 4.53
Control group(n=28)	57.79± 11.48	47.96± 10.12	35.43± 11.48	28.65± 10.32	50.42± 7.41
P value	$P>0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$

Differentials of the thigh circumference between the two thighs presented degressive trend at different times with treatment in both groups, and the differentials in the trial group was less than that in the control group at the same time with treatment. Rate of the thigh swelling remission in trial group was higher than that in the control group.

Note: $P<0.05$ denoted statistical significance.

表 3 两组患者治疗前后患肢与健侧小腿最粗处小腿周径差及消肿率
Table 3 The calf swelling remission rate were evaluated between the two groups after treatment

Groups	Differentials of the calf circumference (mm)				Rate of the calf swelling remission %
	Before treatment	At 3 days after treatment	At 7 days after treatment	At 2 weeks after treatment	
Trial group (n=65)	35.65± 7.74	15.52± 7.91	10.52± 7.91	6.09± 6.39	76.48± 8.24
Control group(n=28)	36.18 ± 8.06	25.23± 7.76	20.47± 7.05	16.30± 7.14	54.95± 8.14
P value	$P>0.05$	$P<0.05$	$P<0.05$	$P<0.05$	$P<0.05$

Differentials of the calf circumference between the two calves also presented degressive trend at different times with treatment in both groups, and the differentials in the trial group was less than that in the control group at the same time with treatment. Rate of the thigh swelling remission in trial group was higher than that in the control group.

Note: $P<0.05$ denoted statistical significance.

2.2 两组患者住院治疗 2 周后下肢深静脉血栓溶通率比较

试验组患肢血栓溶通率 III 级 42.54%(27/65), II 级 51.77%(33/65), I 级 7.69%(5/65), 观察组患肢血栓溶通率 III 级 0%

(0/28), II 级 14.29%(4/28), I 级 85.71%(24/28), III 级和 II 级表示溶栓有效, 试验组有效率为 92.31%(60/65), 显著高于对照组 $[14.29\%(4/28)]$ ($P<0.05$) (表 3)。

表 4 两组患者治疗后下肢深静脉血栓溶通率比较
Table 4 Comparison of the deep vein thrombolysis rate between the two groups after treatment

Deep vein thrombolysis	Trial group (n)	Control group (n)	P value
I	5	24	$P<0.05$
II	33	4	$P<0.05$
III	27	0	$P<0.05$

Note: $P<0.05$ denoted statistical significance.

2.3 两组患者并发症的发生情况比较

试验组 65 例患者均行下腔静脉滤器植入, 其中 1 例因滤器内有较大血栓未能取出, 其余滤器均于植入滤器后两周内取出。溶栓过程中, 穿刺点、牙龈、皮肤、泌尿等出血并发症 3 例, 无重要脏器及颅内出血、无严重肺栓塞、无死亡等严重并发症,

行髂静脉球囊扩张加支架植入 11 例, 随访半年患者髂静脉均通畅。28 例单纯抗凝患者中, 1 例出现因轻度皮下出血。无重要脏器出血、严重肺栓塞、死亡等严重并发症, 随访半年, 无下肢深静脉血栓复发病例。

2.4 两种随访期间的通畅和 PTS 的发生率比较

随访半年后, 试验组患者下肢血管的通畅率为 90.67% (57/65), PTS 率为 7.69% (5/65)。对照组患者下肢血管的通畅率为 21.42% (6/28), PTS 率为 14.28% (4/28)。试验组治疗半年后血管通畅率明显高于对照组 ($P < 0.05$), 而 PTS 发生率明显低于对照组 ($P < 0.05$)。

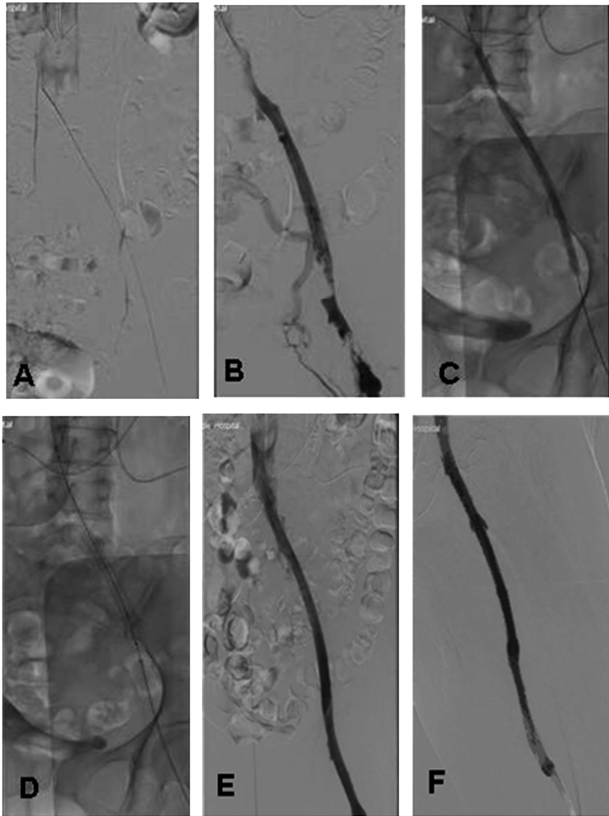


图 1 左下肢深静脉中央型血栓置管溶栓 + 支架置入术

注: A: 滤器及溶栓管植入; B: 溶栓后造影显示髂及股总静脉狭窄;

C: 球囊扩张髂静脉狭窄; D: 球囊扩张后髂静脉置入支架。

E 和 F: 为植入支架后髂静脉段及股静脉段造影通畅。

Fig.1 Thrombolysis and stent placement for deep venous thrombosis of the left lower extremity

Note: A: Implantation of filter and thrombolytic catheter;

B: The left iliac vein and femoral vein were revealed stenosis after thrombolysis; C: Balloon angioplasty demonstrated a waist at the left common iliac vein; D: The left iliac vein was implanted by the stent after balloon dilation; E and F: The left iliac vein and femoral vein were unobstructed after implantation of the stent.

3 讨论

静脉血栓栓塞症(VTE)包括 DVT 和 PE, 每年发病率约 1-2 人/1000, 已经成为主要危害公共健康的疾病。急性 DVT 的近期及远期致死、致残率高, DVT 急性阶段能引起肺动脉栓塞、股青肿、交叉性栓塞。远期并发症包括 VTE 复发、PTS 和慢性血栓性肺动脉高压^[12]。DVT 复发是 VTE 长期的影响, 据报道 10 年的复发率高达 30%^[13,14]。而欧洲预防血栓栓塞事件登记处最近发表的结果显示 25% 的 VTE 易复发^[15]。PTS 是 DVT 的另

一长期并发症, 其特征是慢性的下肢疼痛、肿胀、沉重感、易疲劳、下肢静脉曲张、少数患者会出现淤滞性皮炎、溃疡等。首次发生的 DVT 患者, 即使足量抗凝, 2 年后 PTS 的发生率仍有 20-55%^[9]。已有多项研究评估 DVT 患者发展为 PTS 的危险因素: 首先, 复发的中央型 DVT 增加 PTS 的发生率 2-6 倍^[16]; 其次, 未足量的抗凝也与 PTS 的发展相关^[17]; 再者, DVT 的血栓解剖学范围和 PTS 的发生率及严重程度相关; 中央型 DVT 比周围型 DVT 的 PTS 发生率更高。据报道髂股静脉血栓即使充分治疗, 2 年后的 PTS 的发生率仍超过 50%^[16]。髂静脉血栓患者的 PTS 往往表现为重度的症状, VTE 的复发率高达 2 倍^[16,17]。

抗凝仍然是 DVT 的一线治疗, 这在一定的情况是不足的; 单纯的标准抗凝能抑制血栓蔓延, 降低肺栓塞的发生率, 预防血栓复发, 但不能有效加速溶栓。早期、快速清除血栓, 恢复下肢深静脉的血流通畅可以预防后期静脉返流、静脉回流受阻和 PTS 的发生。这个理论涉及到开放静脉假说, 已经被早期的系统溶栓和血栓切除随机对照研究(RCT)验证^[18,19]。因系统溶栓增加出血风险, 外科手术切除血栓创伤性大, 目前系统溶栓不在用于 DVT 的治疗, 外科手术切除血栓仅用于严重 DVT 而存在腔内治疗禁忌患者^[20]。而 CDT 能提供更优的治疗选择。CDT 是直接带有多个侧孔溶栓导管插入血栓中, 通过增加溶栓药物与血栓的结合位点, 从而提高溶栓效率、减少尿激酶药物剂量、减少治疗期间出血并发症。随着技术的发展和越来越多的试验数据的出现, CDT 腔内介入治疗 DVT 病例也在不断地增多。

早期的研究表明 CDT 治疗下肢深静脉血栓的成功溶栓率达 88%, 更低的 PTS 发生率, 且提高患者的生活质量, 超过 5 年以上的症状缓解^[21]。最有说服力的 CDT 研究是 CaVenT 试验, 发表在 2012 年, 总数 209 例急性髂股静脉 DVT 患者被随机分为单纯抗凝组或 CDT 联合抗凝组, 2 组均接受弹力袜治疗, 在 24 个月后 CDT 联合抗凝组 PTS 的发生率是 41%, 而单纯抗凝组 PTS 的发生率是 55% ($P = 0.047$), CDT 联合抗凝降低 PTS 发生率的 14%, 相对危险度是 26%, CDT 组主要的出血并发症是 3.3%; 最近发表的 5 年随访结果证明 CDT 治疗患者能持续临床获益: 对照组 73% 发生 PTS, 而 CDT 试验组为 43% ($P < 0.0001$), 但是两组患者的生活质量评分没有明显差异^[22]。最近关于急性下肢深静脉血栓的研究, 接触性导管溶栓治疗清除血栓 (ATTRACT 试验) 研究显示: CDT 与单纯抗凝相比并不能减少 PTS 的发生, 但能减轻重度 PTS 发生率^[23]。DUTCH CAVA 试验 (NCT00970619) (导管对比单纯抗凝治疗急性髂股静脉 DVT) 是一个开放的、多中心的、随机试验, 急性髂股静脉 DVT 患者随机分为单纯抗凝组和抗凝联合 CDT 组, 使用 EKOS 系统评估其有效性, 主要的研究指标是在一年后 PTS 发生率, 次要的研究指标包括生活质量改善和后期随访的 PTS 的发生率。这个研究将在 2018 年 12 月得出结论。

本研究结果显示试验组溶栓有效率稍高于早期研究, 可能我们入组的患者血栓发病稍早, 一般血栓形成 72 小时以内的溶栓效果最好, 随着时间的推移, 血栓的组成成分和结构发生变化。因此, 有研究建议溶栓时间一般不超过一周, 所以减少血

栓形成和 CDT 治疗的时间窗至关重要。治疗期间, 试验组早期改善患者下肢肿胀症状效果明显, 溶栓治疗 3 天患者下肢肿胀明显缓解, 出血并发症与对照组相比并未明显增加。随访半年, 试验组患者下肢血管的通畅率明显高于对照组, 而 PTS 发生率显著低于对照组, 提示血栓清除率越高, 后期血管通畅率越高, 而 PTS 的发生率与血管通畅率呈反比。有证据表明髂股静脉 DVT (髂静脉和或股总静脉) 相对于非广泛的近端 DVT 有更高不利的危险因素。当股静脉血栓形成后, 股深静脉变成主要间接渠道。因此, 有时高于股深静脉开口的血栓导致严重的流出道受阻, 引起更加严重的 DVT 首发症状和后期的临床后遗症^[24,25]。

目前, 对于下肢 DVT 患者的治疗, 各个医学会存在相似而不同的观点。美国胸科医师协会(CHEST)承认 CDT 治疗可能使大多 DVT 患者获益, 但是鉴于有限的证据, 应告知患者风险 / 获益率仍然不确定^[26,27]。美国心脏病学会(AHA)推荐 CDT 作为急性的髂股静脉 DVT 患者(症状小于 21 天)或抗凝期间症状进展患者的首选一线治疗^[28]。美国介入放射学会(SIR)推荐 CDT 适用于: (1) 急性髂股静脉 DVT、低出血风险和预期寿命长患者。 (2) 症状明显的亚急性和慢性髂股静脉 DVT 患者。 (3) 急性或亚急性下腔静脉血栓。 (4) 严重威胁下肢动脉循环的血栓, 如股青肿患者。SIR 声明: CDT 可适用于一定类型的急性股腘静脉 DVT, 但是治疗门槛应该比髂股静脉 DVT 门槛更高^[29,30]。

综上所述, 与标准抗凝治疗髂股静脉 DVT 对比, CDT 腔内治疗是安全的, 能快速清除血栓, 更快恢复静脉血流, 减轻患者肿胀、疼痛症状, 减少后期 PTS 的发生。但我们的研究也有一些限制或不足, 如本研究是单中心的回顾性研究, 样本量相对较少, 患者的随访时间短。因此, 后续仍需进一步研究以明确 CDT 腔内治疗用于急性下肢深静脉血栓的远期疗效和安全性。

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