

Posterior tibial vein approach to catheter-directed thrombolysis for iliofemoral deep venous thrombosis



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ABSTRACT

Objective: Deep venous thrombosis (DVT) remains a significant cause of morbidity in the American population. Catheter-directed thrombolysis for acute iliofemoral DVT is an effective therapy not only to restore venous patency but also to reduce the development of post-thrombotic syndrome (PTS), especially in patients with extensive thrombosis involving the iliac and femoral venous segments. We hypothesized that delivery of thrombolytics through an access site in a vein distal to the segments containing thrombus would provide the greatest short- and long-term therapeutic clinical benefit with similar safety and efficacy.

Methods: All patients treated at a single institution between 2009 and 2016 undergoing mechanical and chemical thrombolysis for iliofemoral DVT were retrospectively reviewed. Patients were divided into groups by access site, including contralateral and ipsilateral femoral vein, popliteal vein, and posterior tibial vein (PTV). Preoperative demographics, intraoperative data, and postoperative outpatient charts were analyzed. Primary end points included evidence of incompetence after the procedure by duplex ultrasound assessment and development of complications of PTS as defined by the Villalta scale.

Results: Fifty-eight patients underwent mechanical and chemical thrombolysis, and 51 patients met the inclusion criteria. Thrombolysis access was through PTV (n = 27), popliteal vein (n = 20), or femoral vein (n = 4). More patients were female (55%), and the mean age was 57 years. Forty patients had unilateral DVT, whereas 11 patients had bilateral involvement. After lysis, 44 patients underwent percutaneous venous angioplasty and 11 patients underwent venous stenting in the acute setting. Although not statistically significant, mean operative times were slightly longer in the posterior tibial approach (156.7 minutes vs 130.6 minutes; $P = .08$), and mean fluoroscopy time was higher in the posterior tibial group (18.1 minutes vs 14.3 minutes; $P = .17$). Overall 90-day morbidity was 9.8%, and no deaths were recorded. Patency of the deep venous system was similar between the posterior tibial and the popliteal or femoral approach (95% vs 88%; $P = .29$); 21.6% developed symptoms of PTS. There was no difference for development of PTS between posterior tibial and popliteal or femoral approaches (22% vs 20.8%; $P = .52$). There was no difference in development of chronic nonocclusive DVT (37% vs 35%; $P = .61$). Median follow-up was 8.7 months (range, 0.4-58.9 months).

Conclusions: The PTV approach to catheter-directed thrombolysis is a safe and sensible option for the treatment of iliofemoral and femoropopliteal DVT. A larger cohort will be necessary to demonstrate superiority of tibial vein access in the treatment of iliofemoral DVT with popliteal involvement. (*J Vasc Surg: Venous and Lym Dis* 2019;7:629-34.)

Keywords: Posterior tibial vein; Ilio-femoral deep venous thrombosis; Catheter-directed thrombolysis

Acute deep venous thrombosis (DVT) of the lower extremities is a common disease that is associated with significant morbidity. The estimated incidence of DVT is

approximately 1 in 1000, with nearly 250,000 new cases each year.¹ The increased incidence of DVT seems to correlate with a more effective diagnosis, the aging population, and the traditional risk factors (stasis, injury, and hypercoagulability) recognized by Virchow more than 150 years ago.² It is generally accepted that the most serious acute complication of DVT is pulmonary embolism (PE).³

It is recognized that post-thrombotic syndrome (PTS), the long-term sequela of DVT that can result in debilitating edema, ulceration, and dermatosclerosis, is a serious health risk with significant loss of function and productivity.⁴ Prevention of PTS should be a priority in the management of iliofemoral DVT. Our team was an early adopter of the various technologies aimed at early resolution of acute proximal and femoral DVT with the expectation that the long-term complications could be avoided or mitigated by aggressive intervention. Undoubtedly, the emphasis on DVT prevention is key to

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avoiding many complications, but patients still develop DVT and PE. Current treatment regimens have been directed at preventing the development of PTS by attempting to restore competence of venous segment valves and luminal patency.

Studies have shown that catheter-directed thrombolysis (CDT) is a safe and potentially efficacious treatment of acute iliofemoral DVT.^{5,6} Younger patients and those with a more significant burden of thrombus have been shown to benefit more with CDT.^{4,7,8} Our working hypothesis has centered on the premise that acute thrombus is simpler to clear with current treatment modalities and complete clearance would provide the best clinical outcomes.⁷ We employed venous access through the ipsilateral popliteal vein (PV) or the contralateral femoral vein (FV) in our early clinical experience and found the ability to clear thrombus from all involved venous segments inadequate. Therefore, we began accessing the posterior tibial veins (PTVs) in an attempt to clear all major deep axial veins of acute thrombus. Without adequate tibial vein drainage into the PVs or femoral drainage into the common FVs, venous flow rates are too limited to maintain patency after thrombolysis.⁹ Although the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial recently showed no decreased risk of PTS for all patients undergoing CDT, CDT remains a significant therapeutic option for those with extensive proximal iliofemoral DVT to mitigate the long-term sequelae.^{6,7}

Either FVs or PVs are considered standard venous access points for patients undergoing CDT for iliofemoral DVT regardless of DVT extent. Studies have also reported other venous accesses with great saphenous vein and small saphenous vein approaches.^{3,10} Armon et al¹¹ first described a PTV approach to CDT for DVT. There are no long-term outcomes data regarding use of the PTV as an approach to CDT for iliofemoral DVT. We hypothesized that PTV cannulation would have significantly improved short- and long-term outcomes for treatment of acute iliofemoral DVT and femoropopliteal DVT compared with standard access sites without significant morbidity because access for the delivery of thrombolytics is expected to be more effective when infused distal to the thrombus burden. We believe that the PTV approach to CDT is both safe and efficacious for the treatment of iliofemoral DVT.

METHODS

The study protocol was approved by the Institutional Review Board at Providence-Providence Park Hospital. A retrospective review of all patients undergoing CDT for acute iliofemoral DVT regardless of extent of thrombus burden at both Ascension Providence Hospital and Providence Park Hospital between June 2009 and February 2016 was performed. Approval from our

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Fifty-one patients underwent catheter-directed thrombolysis by various approaches for iliofemoral deep venous thrombosis (DVT). Overall 90-day morbidity was 9.8%, and there were no deaths. There was no difference in chronic, nonocclusive DVT or post-thrombotic syndrome by access (22% with posterior tibial approach, 20.8% with popliteal or femoral approach).
- **Take Home Message:** Posterior tibial vein access appears to be safe and efficacious for catheter-directed thrombolysis for treatment of iliofemoral or femoropopliteal DVT.

Institutional Review Board was completed before data collection. Informed consent of the patient was not required as this study required only retrospective chart review. Patients were identified by *International Classification of Diseases* code 99.10 for injection or infusion of thrombolytics. Patients with no documented follow-up were excluded from this study.

All patients had the diagnosis of an acute iliofemoral DVT by various imaging modalities, including venous duplex ultrasound, venous computed tomography, ascending venography, and a combination of these diagnostic studies. The presence of unilateral and bilateral iliofemoral DVT was noted. Proximal and distal extents of DVT were recorded, including inferior vena cava (IVC), iliac vein, FV, PV, and PTV. Secondary diagnoses were recorded to be considered in data analysis, which included phlegmasia, IVC thrombosis, and May-Thurner syndrome. The diagnosis of phlegmasia resulted from clinical assessment and was complemented by duplex ultrasound that revealed the extent of the thrombosis. The diagnosis of May-Thurner syndrome was generally based on imaging results from either venous computed tomography or ascending venography that demonstrated compression of the left common iliac vein by the right common iliac artery. No patients in this study underwent intravascular ultrasound as this was not available at our institution until after this study was completed. Preoperative demographics data collection as recorded in the medical record included age, sex, comorbidities, smoking status, history of IVC filter, and prior DVT or PE.

Patients underwent CDT with use of an EKOS device (EKOS Corporation, Bothell, Wash) for both mechanical and pharmacologic thrombolysis. All venous access sites were accessed with ultrasound guidance. Nearly all patients completed the procedure under local anesthesia with intravenous sedation. Alteplase infusion dosing was either 1 mg or 2 mg per hour and titrated

to guidelines monitoring hemoglobin and fibrinogen levels. All patients received a heparin infusion of 500 units/h through the side port of the access sheath during lysis. Serial coagulation panel and fibrinogen levels were monitored in the intensive care unit. Almost all patients underwent at least one additional procedure after the index procedure to assess effectiveness of therapy and need for additional intervention before cessation of CDT. Operative and fluoroscopy times were recorded for all index and follow-up procedures. Access site, largest size sheath, and laterality were recorded. When appropriate, patients underwent venous angioplasty or stent placement in the acute setting. All patients were monitored in the intensive care unit perioperatively.

Patients were divided into groups by access site: contralateral and ipsilateral FV and PV and PTV. The access site was chosen initially on the basis of the surgeon's preference and later by the distal extent of the thrombus in the affected limb.

Primary end points included evidence of venous patency and venous incompetence by duplex ultrasound and development of complications of PTS. PTS was defined by a Villalta scale score of >5. A score of 5 to 9 signifies mild disease; 10 to 14, moderate disease; and ≥15, severe disease. The Villalta scale has been validated and is reported to be a reliable method of identifying and quantifying PTS.¹²

The 90-day morbidity and 30-day mortality were recorded. Morbidity was defined as perioperative adverse events that significantly affected the patient's outcome based on the Clavien-Dindo classification. All patients were maintained on systemic coagulation with an oral agent or enoxaparin (Lovenox) for a duration of at least 6 months. Follow-up venous duplex ultrasound scans were performed in the standing position with documentation of residual thrombus burden, restoration of venous patency through flow and compression, and venous competence with reflex <500 milliseconds. Presence of

PTS postoperatively at follow-up was considered if it was documented on follow-up clinic appointments. The degree of PTS was divided into mild, moderate, and severe. Median follow-up was recorded.

Statistical analysis was completed using Microsoft Excel (Microsoft, Redmond, Wash). Descriptive characteristics are reported as mean ± standard deviation. Dichotomous covariates between the groups were compared using the Fisher exact test. A *P* value of < .05 was considered statistically significant. Our study was based on the number of patients who had undergone CDT rather than a difference in outcome. No power analysis was completed as this was a pilot study, and there are no data in the literature that can be used as a starting point for sample size analysis.

RESULTS

Fifty-one patients undergoing mechanical and chemical thrombolysis for iliofemoral DVT met inclusion criteria. Seven patients were excluded because of no follow-up recorded. There was no difference in comorbidities or perioperative complication rate within the excluded group. Access was through the PTV in 27 patients, through the PV in 20 patients, and through the FV in 4 patients. Mean age of the patients was 57 years; 51% were female. Seventy-four percent of all patients had prior history of DVT or PE. Hypertension was the most common comorbidity and was recorded in 49% of the patients, with the PV/FV group being statistically significantly higher (*P* = .02). There were no other statistical differences between the groups in identified comorbidities (Table 1). Fourteen patients had a history of previous IVC filter placement.

All patients had venous duplex ultrasound imaging to establish the diagnosis of acute iliofemoral DVT. Twenty-six patients had computed tomography as additional diagnostic testing (mainly to assess the proximal extent of the thrombus or tumor obstruction or to evaluate the IVC filter). All patients had ascending

Table 1. Demographics

	All (N = 51)	PTV (n = 27)	POP/FV (n = 24)	<i>P</i> value
Age, years, mean	57	56	59	.30
Female	28 (55)	12 (44)	16 (67)	.11
Comorbidities				
History of DVT or PE	38 (74)	20 (74)	18 (75)	.94
Hyperlipidemia	16 (31)	6 (22)	10 (42)	.13
Diabetes mellitus	10 (20)	4 (15)	6 (25)	.36
Hypertension	25 (49)	9 (33)	16 (67)	.02
COPD	5 (10)	2 (7)	3 (12)	.54
Smoking	18 (35)	11 (41)	7 (29)	.39

COPD, Chronic obstructive pulmonary disease; DVT, deep venous thrombosis; PE, pulmonary embolism; POP/FV, popliteal and femoral veins; PTV, posterior tibial vein.
Categorical variables are presented as number (%).

venography. The most common secondary diagnosis at the time of CDT was phlegmasia alba or phlegmasia cerulea dolens, which was documented in 30 patients. All patients suffered with some component of congestive edema, but the diagnosis of phlegmasia was significantly higher in the PTV group (70% vs 46%; $P = .08$), although not statistically significant represents the justification by our team to aggressively clear all thrombus from the axial veins of the affected limb. May-Thurner syndrome (seven patients) and IVC thrombosis (nine patients) were also recorded as secondary diagnoses. Twenty-seven patients had unilateral left lower extremity DVT, whereas 13 patients had unilateral right lower extremity DVT. Eleven patients had bilateral disease requiring intervention on each limb (Table II).

All patients included in our cohort had thrombus burden that involved the iliofemoral venous segments; 42 patients had PV involvement, 33 patients had IVC involvement, and 20 patients had PTV involvement. There was significantly higher involvement of both the PV (93% vs 71%; $P = .04$) and PTV (74% vs 0%; $P < .01$) in the PTV group compared with the PV/FV group. All patients underwent index CDT in a hybrid suite, and ultrasound was used for initial access. The majority of patients had either one or two subsequent procedures for both assessment of therapy and percutaneous intervention. There were 43 patients who underwent only one lysis check, whereas 11 patients required additional assessments. Fifty patients were able to undergo CDT under local anesthesia with intravenous sedation. Only one patient required general anesthesia with endotracheal intubation secondary to being approximately 8 weeks pregnant at the time of the procedure.

Mean procedural time of the index CDT was 85.9 minutes in the PV/FV group compared with 106.5 minutes in the PTV group ($P = .08$). Total procedural time, which

is the summation of index and follow-up procedures for the individual patient, was higher in the PTV group (156.7 minutes vs 130.6 minutes; $P = .08$) and correlates with the more extensive nature of the DVT. Both mean fluoroscopy time for the index procedure and total fluoroscopy time were higher in the PTV group compared with the PV/FV group (18.1 minutes vs 14.3 minutes; $P = .17$). Median largest sheath used was similar between the two groups, with 7F used in the PV/FV group (range, 5F-11F) and 8F used in the PTV group (range, 5F-11F). After CDT, 44 patients underwent percutaneous angioplasty and 11 patients underwent venous stenting; 33 patients underwent venous angioplasty alone. All 11 stents were placed in the common iliac or external iliac veins.

Mean hospital length of stay was similar between groups (7.6 vs 8.0 days; $P = .44$), which represents both the initial evaluation and the treatment regimens. All patients were maintained on systemic anticoagulation postoperatively (41% for 6-month duration and 43% life-long). Overall 90-day morbidity was 9.8%, and no deaths were recorded within 30 days. Median outpatient follow-up was 8.7 months (range, 0.4-58.9 months).

Thirty-six patients underwent venous duplex ultrasound scanning during outpatient follow-up. Overall venous patency by duplex ultrasound assessment was 91.7%. There was no significant difference in venous patency between the PTV and PV/FV groups (94.7% vs 88.2%; $P = .29$). Persistent nonocclusive or chronic DVT was present in 36.1% of patients, and there was no difference between groups. Many patients had a prior history of DVT, and the chronicity was not recorded. Twenty-four patients had venous duplex ultrasound imaging that included evaluation for venous incompetence. Eight patients in the PTV group had evidence of venous incompetence, whereas four patients in the PV/FV groups had

Table II. Intraoperative and postprocedural outcomes

	All (N = 51)	PTV (n = 27)	POP/FV (n = 24)	P value
Bilateral disease	11 (22)	5 (18)	6 (25)	.57
IVC involvement	33 (65)	17 (63)	16 (67)	.78
PV involvement	42 (82)	25 (93)	17 (71)	.04
PTV involvement	20 (39)	20 (74)	0	<.01
Phlegmasia	30 (59)	19 (70)	11 (46)	.08
May-Thurner syndrome	7 (14)	3 (11)	4 (15)	.56
IVC thrombosis	9 (18)	3 (11)	6 (25)	.19
OR time, minutes, mean	144.4	156.7	130.6	.08
Fluoroscopy, minutes, mean	16.3	18.1	14.3	.17
PTS, %	21.6	22	20.8	.52
Venous patency, %	91.7	94.7	88.2	.29
Chronic DVT, %	36.1	36.8	35.3	.61

DVT, Deep venous thrombosis; IVC, inferior vena cava; OR, operating room; POP/FV, popliteal and femoral veins; PTS, post-thrombotic syndrome; PTV, posterior tibial vein; PV, popliteal vein.
Categorical variables are presented as number (%).

venous incompetence. Eleven patients developed PTS as defined by a Villalta scale score of >5 . There was no difference between PTV and PV/FV groups for PTS (22% vs 21%; $P = .52$).

Three hemorrhagic complications were recognized in the immediate periprocedural period. Each bleeding complication occurred in the PV/FV group. One patient developed a retroperitoneal hematoma that required cessation of systemic anticoagulation and IVC filter placement. Two bleeding complications resulted from post-procedure systemic anticoagulation; one postpartum patient developed a perineal hematoma and required cessation of anticoagulation, and the other patient had upper gastrointestinal bleeding and required cessation of anticoagulation with placement of an IVC filter. There were no local bleeding complications in the PTV group.

DISCUSSION

Traditional treatment of lower extremity DVT continues to center on systemic anticoagulation therapy. The primary goal of medical therapy is prevention of subsequent PE and propagation of the thrombus burden within the affected vein. With extensive lower extremity DVT and proximal iliofemoral thrombus, patients are more likely to develop long-term symptoms of chronic venous insufficiency and PTS.⁷ Thrombus burden, residual thrombus, and recurrent DVT are strong predictors of subsequent PTS.⁷ CDT in iliofemoral DVT allows improved thrombus resolution with restoration of venous valvular function, which has been shown to decrease development of PTS.^{5,7} In a retrospective study of 26,958 patients with DVT or PE, the development of PTS was associated with a 32% increase in annualized total health care costs, in large part due to outpatient resource utilization and the management of venous ulcers.¹³

Our data clearly show that multiple venous access sites are both feasible and safe for CDT for iliofemoral DVT. The PTV access to CDT was first described by Armon et al¹¹ as a new approach to iliofemoral DVT lysis. It was thought that accessing the venous system distal to the PV, which is generally involved with thrombus burden, may improve lysis of the distal segments. Antegrade access to the affected extremity is favored as this allows easier traversal of the valves and is less likely to damage them inadvertently. There is evidence that the early use of CDT does not adversely affect venous valvular function.¹⁴

A variety of venous access approaches have been described for CDT access for lower extremity DVT. Duan and Ni³ described different approaches for CDT for lower extremity DVT. They compared approaches from small saphenous vein, great saphenous vein, and PV. Their cohort showed that the small saphenous vein approach had more frequent complications than the great saphenous vein approach; however, they did not follow outcomes or development of PTS in this cohort. Ultrasound guidance for direct venous access for CDT is

now commonly used and has become a standard of care in our practice.

Fiengo et al¹⁰ described a saphenous vein 2-year follow-up study with 91% patency results in a 22-patient cohort. Liu et al¹⁵ described below-knee access for CDT for acute entire limb DVT. They showed overall patency of 80.4% and PTS rate of 30.4%.

One possible explanation that the ATTRACT trial failed to clearly identify a reduction in PTS is that the protocol did not mandate attempts to clear the entirety of the thrombus burden from the key affected vessels—PV and FV. Although our numbers were too small to demonstrate superiority of PTV access, we believe the data suggest that PTV access is as effective as traditional access points. We suggest secondary analysis of the ATTRACT trial data to understand the relationship of the extent of thrombus and access site.⁶

Extent of thrombus burden should guide the best approach for venous access in treatment by CDT. Ipsilateral FV and PV approaches have the disadvantage of leaving potential residual thrombus burden after thrombolysis. PTV access provides a more distal point of entry to the deep venous system when it is not involved by thrombus burden in patients with iliofemoral DVT and more distal infrapopliteal disease. PTV access has the advantage with patient positioning during the procedure as the patient may be placed in the supine position. Access to the PV requires the patient to be in the prone position.

When the PTV is used as the venous access point, there appears to be no limit to the proximal extent of thrombus clearance in the IVC or iliac veins. We found no increased rate of complications related to thrombus clearance through the PTV approach.

Procedural time and radiation use were both higher in the PTV group, which we attribute to the complex endovascular maneuvers required in gaining proximal access of the catheter tip in the PTV group and the more extensive thrombus burden.

The clinical symptoms and signs of phlegmasia were more prevalent in the PTV group, and we attribute this observation to the more extensive thrombus burden at presentation. Patients with extensive thrombus burden that extends from the iliofemoral to the popliteal-posterior tibial venous junctions are at higher risk for development of phlegmasia because of lack of collateral venous drainage, especially at the important confluence of veins at both the popliteal and common femoral zones.⁹ The extensive thrombus burden is associated with a more critical clinical presentation and development of symptoms of phlegmasia featured by progression to cyanosis of the extremity. Both PV and PTV were more likely to be involved with thrombus burden in the PTV group compared with the PV/FV group. Grewal et al¹⁶ showed that the degree of thrombus lysis directly correlated with long-term outcomes in development of PTS for patients with extensive DVT treated with CDT.

Primary end points for postprocedural outcomes for index CDT include venous patency or competence by venous duplex ultrasound and development of PTS by survey. Our study showed equivalent rates of venous patency between the two approaches. Our reported patency rates are comparable to those of other studies using this approach. Overall PTS rate for this group was 21.6%; other studies noted a rate as high as 43%.⁵ Venous incompetence was similar in both groups.

We believe the PTV approach has the ability to clear thrombus from the PVs, which may allow more effective tibial venous outflow from the affected calf. Raju et al¹⁷ assessed residual thrombus after CDT. Recurrent thrombosis as well as incidence of PTS appears to be related to residual thrombus burden. This puts extreme importance on fully clearing both the proximal iliac veins and the distal femoropopliteal veins. Despite the low numbers in our cohort, we believe that effective thrombus clearance leads to improved venous drainage and decreased incidence or severity of PTS.

Postprocedural local access site complications were negligible in the PTV group. In one patient with access through the FV, retroperitoneal bleeding developed, requiring cessation of anticoagulation and subsequent placement of an IVC filter. The PTV access approach is relatively safe, with no significant risk for bleeding, despite its proximity to the posterior tibial artery, and it requires only the skills of ultrasound-guided venous cannulation to treat symptomatic varicosities by ablation.

Limitations of this study include small population size at a single institution. Lack of long-term follow-up may also limit the potential identification of patients who may develop venous incompetency, PTS, and recurrence. Our small population size also allows type II error in our analysis.

CONCLUSIONS

The PTV approach to CDT is a safe and sensible option for the treatment of iliofemoral and femoropopliteal DVT. A larger cohort will be necessary to demonstrate superiority of tibial vein access in femoropopliteal DVT. Further secondary analysis of the ATTRACT trial may be of benefit to evaluate effective thrombus clearance from the common FV and PV.

AUTHOR CONTRIBUTIONS

Conception and design: SDB, RN, SB, WO
 Analysis and interpretation: SDB, RN, SB, WO
 Data collection: SDB, RN
 Writing the article: SDB, RN
 Critical revision of the article: SB, WO
 Final approval of the article: SDB, RN, SB, WO
 Statistical analysis: SDB
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 Overall responsibility: SDB

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