European Journal of Vascular and Endovascular Surgery 44 (2012) 210–213

Contents lists available at SciVerse ScienceDirect

European Journal of Vascular and Endovascular Surgery

journal homepage: www.ejves.com

Quantity of Residual Thrombus after Successful Catheter-directed Thrombolysis for Iliofemoral Deep Venous Thrombosis Correlates with Recurrence☆

F. Aziz [a], A.J. Comerota [a,b,*]

[a] Jobst Vascular Institute, 2109 Hughes Dr, Suite 400, Toledo, OH 43606, USA
[b] Adjunct Professor of Surgery, University of Michigan, Ann Arbor, MI 48109, USA

WHAT THIS PAPER ADDS

- Most patients with extensive proximal (iliofemoral) deep venous thrombosis (DVT) continue to be treated with anticoagulation alone, despite a growing body of evidence demonstrating improved outcomes with a strategy of thrombus elimination. This study contributes to the existing literature by focussing on the reduced likelihood of DVT recurrence as a consequence of eliminating thrombus from the deep veins of the lower extremity.

ARTICLE INFO

Article history:
Received 30 September 2011
Accepted 21 April 2012
Available online 31 May 2012

Keywords:
Catheter-directed thrombolysis
Iliofemoral DVT
Recurrent DVT
Residual thrombus

ABSTRACT

Objectives: Iliofemoral deep venous thrombosis (IFDVT) is an independent risk factor for recurrent DVT. It has been observed that recurrent DVT correlates with residual thrombus. This study evaluates whether risk of recurrence is related to the amount of residual thrombus following catheter-directed thrombolysis (CDT) for IFDVT.

Methods: Patients who underwent CDT for IFDVT had their degree of lysis quantified by a reader blind to the patients' long-term clinical outcome. Patients were classified into two groups, ≥50% and <50% residual thrombus. Recurrence was defined as a symptomatic presentation with image verification of new or additional thrombus.

Results: A total of 75 patients underwent CDT for IFDVT. Median follow-up was 35.9 months. Sixty-eight patients (91%) had no evidence of recurrence and seven (9%) developed recurrence. Of the patients who had ≥50% (mean 80%) residual thrombus, 50% (4/8) experienced recurrence, but in those with <50% (mean 35%) residual thrombus, only 5% (3/67) had recurrent DVT ($P = 0.0014$).

Conclusion: The burden of residual thrombus at completion of CDT correlates with the risk of DVT recurrence. Patients having CDT for IFDVT had a lower risk of recurrence than expected. Successful clearing of acute clot in IFDVT patients significantly reduces the recurrence risk compared to patients with a large residual thrombus burden.

The iliofemoral segment of the venous system is the single outflow channel for the lower extremity. Occlusion of this outflow tract leads to high venous and compartment pressures acutely,[1] and increased venous pressures and post-thrombotic morbidity as long-term sequelae.[2] The post-thrombotic syndrome (PTS), a debilitating condition that reduces health-related quality of life,[3] occurs more frequently in patients following ipsilateral recurrent deep venous thrombosis (DVT). Iliofemoral DVT (IFDVT) is associated with a higher risk of recurrence than infrainguinal DVT, reaching 12% at 3 months.[4] Each episode of recurrence increases the severity of the PTS.[5] In addition to its more proximal location, a significantly greater thrombus burden differentiates IFDVT from infrainguinal DVT.

Strategies of thrombus removal have been selectively offered to patients with extensive DVT in an attempt to reduce post-thrombotic morbidity. Venous thrombectomy has shown better results than anticoagulation alone for patients with IFDVT,[6–8] but

☆ Presented at the American Venous Forum, 24 February 2011 (Winner, 2011 Servier Traveling Fellowship).

* Corresponding author. A.J. Comerota, Jobst Vascular Institute, 2109 Hughes Dr, Suite 400, Toledo, OH 43606, USA. Tel.: +1 419 291 2080; fax: +1 419 479 6980.
E-mail address: marilyn.gravett@promedica.org (A.J. Comerota).

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doi:10.1016/j.ejvs.2012.04.016

most vascular surgeons have not embraced it. Catheter-based thrombolytic therapy performed with current techniques has been associated with success in 70–90% of cases with reduced risk of bleeding.[9–12] Successful catheter-directed thrombolysis (CDT) for IFDVT has been associated with a reduction in thrombus burden and PTS and, as a result, improved quality of life.[13] Baekgaard et al.[12] reported a lower than expected recurrence rate 6 years following CDT for acute IFDVT. One might expect that patients with lesser amounts of thrombus after catheter-based thrombolysis will have a lower risk of recurrent DVT.

The purpose of this study is to determine the rate of recurrent DVT in patients with IFDVT treated by catheter-based techniques of thrombus removal and to assess whether recurrence correlates with the amount of residual thrombus at the completion of CDT.

Methods

Consecutive patients with symptomatic acute DVT involving the iliofemoral or vena caval segments (with or without infrainguinal DVT) who were treated with CDT form the basis of this study. This study was approved by the institutional review board.

Access for CDT was obtained with ultrasound guidance into the ipsilateral popliteal vein, common femoral vein and/or posterior tibial vein, depending upon the location and extent of thrombosis. Vena caval imaging was performed in all patients to assess whether thrombus extended into or involved the vena cava. Vena caval filters were placed in approximately 30% of patients prior to CDT. They were uniformly used in patients with free-floating thrombus in the inferior vena cava and at the discretion of the interventionalist.

The details of the technique of CDT have been previously reported.[14] Briefly, patients were treated with recombinant tissue plasminogen activator (rt-PA) at a dose of 1–1.5 mg h^{-1} depending on thrombus volume and number of catheters used. The concentration of rt-PA varied from 1 mg/50 cc to 1 mg/100 cc NaCl. Pharmacomechanical thrombolysis was integrated into patient care as these techniques became available. These procedures used rheolytic, isolated segmental and/or ultrasound-accelerated lytic catheters.

Rheolytic thrombectomy was used for segmental thrombus. Isolated, segmental pharmacomechanical thrombolysis became the preferred initial approach to reduce thrombus burden. This technique uses the double-balloon Trellis® catheter (Covidien, Mansfield, MA, USA) to segmentally dissolve and macerate the thrombus. Residual thrombus was treated with the standard drip technique.

Following lysis, balloon catheters were used as needed to dilate areas of stenosis, except in the case of an iliac vein stenosis, where balloon venoplasty and stenting were performed to ensure unobstructed venous drainage from the common femoral vein into the vena cava.

CDT was terminated when maximal benefit from the procedure was obtained, as determined by the treating physician, increased concern for bleeding, clinical bleeding or patient request. CDT using the drip technique alone often continued 48–72 h and occasionally longer. Since the integration of pharmacomechanical techniques, no treatment time has exceeded 24 h.

Intravascular ultrasound was not used in the management of these patients. Serial ultrasound examinations were not performed during the course of treatment; however, they were performed upon patient presentation, prior to discharge, and during follow-up.

Following CDT, all patients were therapeutically anticoagulated with intravenous unfractionated heparin (UFH) or subcutaneous enoxaparin and converted to oral anticoagulation with warfarin. The duration of anticoagulation was generally longer than that recommended by existing guidelines,[15] with nearly all patients treated for 1 year and many longer if bleeding risk was low and the patient was compliant.

The degree of clot lysis was retrospectively evaluated by review of the phlebograms performed before and after treatment using a modification of the venous scoring method described by Mewissen et al.[9] and previously reported by Martinez et al.[16] Nine venous segments (inferior vena cava, common iliac, external iliac, common femoral, proximal femoral, distal femoral, popliteal, tibial and profunda femoris veins) were analysed and scored as follows: 0, thrombus-free (normal) segment; 1, 1–49% luminal reduction by thrombus and/or stenosis; 2, 50–99% luminal reduction; and 3, occluded. The percent of clot lysed was calculated by subtracting the post-treatment thrombus score from the pretreatment thrombus score and dividing by the pretreatment score. The physician interpreting the phlebograms was blinded to the clinical outcomes of the patients, and the physician performing the clinical evaluation and treating the patient's recurrence was not aware of the patient's phlebographic score.

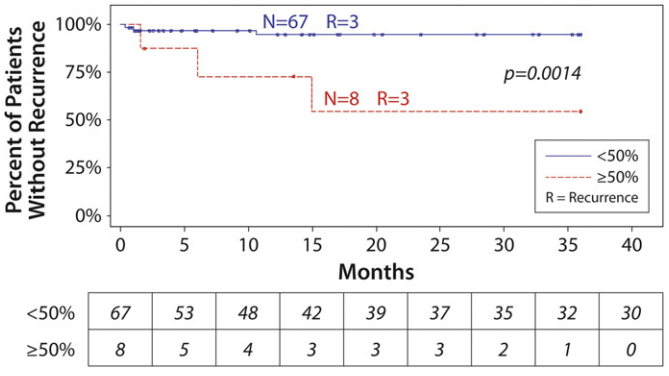
Patients were grouped by quantity of residual thrombus: ≥50% residual thrombus versus <50% residual thrombus. All were followed up with serial clinical examinations and venous duplex ultrasounds. Recurrence was defined by patients presenting with symptoms of recurrent pain and/or swelling, the presence of a new noncompressible vein segment previously free of thrombus on duplex ultrasound, extension of a previous filling defect into a previously uninvolved segment or a new intraluminal filling defect that was viewed in two or more projections on venogram.

Due to the small number of cases in this study, we used the nonparametric log-rank test rather than the asymptotic chi-squared test to compute the *P*-values.

Results

Seventy-five patients underwent CDT for IFDVT. The mean age of the patients was 48 years and 32 (43%) were female and 43 (57%) male. Mean duration of follow-up was 35 months and the median was 35.9; the interquartile (IQR) range was 44 months. Patients who had pharmacomechanical thrombolysis had better lytic outcomes than those having the drip technique alone. These data were addressed in a previous publication.[16]

Seven (9%) patients developed recurrent DVT, six within 3 years and one at 6.5 years. The 3-year recurrence rate was 8% (6/75).[16] Eight patients had ≥50% residual thrombus (mean 80%) and 67 patients had <50% (mean 35%). The recurrence rate at 3 years among the group of patients with ≥50% residual thrombus was 38% (3/8), and the overall recurrence rate was 50% (4/8). One patient developed recurrent DVT 6.5 years after the initial event. The recurrence rate at 3 years and overall recurrence for those with <50% residual thrombus was 5% (3/67; $P = 0.0014$) (Fig. 1).



<50%	67	53	48	42	39	37	35	32	30
≥50%	8	5	4	3	3	3	2	1	0

Figure 1. Kaplan–Meier curve illustrates correlation between percent of residual thrombus and recurrence of DVT in a 3-year period.

Discussion

This study shows that patients with IFDVT treated with CDT have fewer recurrences when compared to previous reports of IFDVT patients treated with anticoagulation alone[4] and that patients with a greater volume of residual thrombus when CDT was completed were at a higher risk for recurrence. Prior studies have shown a correlation of thrombus volume with recurrence. Douketis et al.[4] followed 1149 patients with acute DVT treated with anticoagulation alone and reported that patients with IFDVT had a 12% 3-month rate of recurrence, a rate 2.4× patients with infrainguinal DVT. The authors concluded that IFDVT was an independent predictor of recurrence.

The observations reported in this study show that a catheter-based strategy of thrombus removal reduces the high rate of recurrence and suggests that the quantity of residual thrombus at completion of CDT directly correlates with recurrent episodes of DVT. When a high degree of clot lysis is achieved, patients have fewer recurrences.

Further support for these observations was provided by Prandoni and colleagues[17] when they performed a prospective study of 313 patients with proximal DVT who were treated with anticoagulation alone. Their patients represented the spectrum of acute DVT, not just IFDVT. When venous duplex ultrasounds were reviewed after the discontinuation of anticoagulation, 70% of patients with obstruction on venous duplex had a recurrence rate compared to 29% of patients with no evidence of residual thrombus. The authors found that residual luminal obstruction was an independent predictor of recurrence (HR 2.4, 95% CI:1.3–4.4; $P = 0.004$).

The REVERSE investigators,[18] who followed up patients with acute DVT treated with anticoagulation alone, failed to confirm a statistical association of residual luminal abnormalities on ultrasound at the time anticoagulation was discontinued with recurrence. They found a 40% increased risk of recurrence with a positive compression ultrasound; although not reaching significance, the point estimate supports the concept.

Tan et al.[19] performed a systematic review and concluded that residual venous thrombosis was a significant predictive factor for recurrence. Similar findings were observed in a prospective study by Piovella et al.[20] in which the authors monitored 283 patients with proximal DVT with serial duplex ultrasounds over a 12-month period. All patients were treated with anticoagulation alone. Within 1 year, 7.1% of patients had recurrent DVT. Eighty percent of patients with DVT recurrence had residual thrombus. The odds ratio for recurrent DVT due to residual thrombus in cancer-free patients was 11.29 at 3 years ($P = 0.002$).

There is a difference between residual thrombus following CDT and findings on compression ultrasound many months later at a time when anticoagulation is terminated. The phlebographic images showing luminal defects at the completion of CDT more likely represent thrombus, while the findings on the ultrasound images months or years later represent intraluminal fibrosis. Although not equivalent structurally, residual thrombus leads to intraluminal fibrosis, and it is reasonable to conclude that the larger the burden of residual thrombus following CDT, the greater the subsequent intraluminal fibrosis.

From a pathophysiologic standpoint, the characteristic distinguishing IFDVT from DVT in other locations is the volume of thrombus. Therefore, thrombus burden in patients with IFDVT may provide a clinically relevant predictor for recurrent DVT. A growing body of evidence suggests the importance of thrombus burden in determining the long-term sequelae of IFDVT.[12,14,21,22]

Breddin et al.[23] conducted a multicentre randomised controlled trial comparing the efficacy of low-molecular-weight heparin (Raviparin) to unfractionated heparin in 1148 patients with acute DVT. Patients were diagnosed with an initial phlebogram and underwent a repeat phlebogram 3 weeks later. One of the secondary end points was recurrent venous thrombo-embolism (VTE). The authors found a statistical correlation ($P = 0.0011$) between the amount of residual venous thrombus on phlebography and subsequent recurrence.

Hull et al.[24] performed a meta-analysis of studies correlating the quantity of residual thrombus to subsequent recurrence. The results favoured a correlation between degree of clot burden and recurrent VTE episodes (RR 0.56, 95% CI 0.42–0.56; $P < 0.001$). The aggregate analysis showed a striking predictive correlation for thrombus burden change and subsequent recurrent VTE episodes ($P = 0.005$).

Patients with symptomatic IFDVT represent a subset of lower extremity DVT patients with large thrombus burdens. It makes intuitive sense that reduction in the amount of clot should reduce recurrence. Our study shows that not all patients treated with CDT for IFDVT have elimination of their clot and that those with high degrees of residual vein thrombus were more prone to recurrence.

Incorporating pharmacomechanical methods during CDT improves outcomes, shortens treatment time and uses lower doses of rt-PA. Martinez et al.[16] reported significantly better treatment results, a 58% reduction in treatment times, and a 44% reduction is dose or rt-PA.

Thrombophilia evaluations were not performed in all patients. Initially, thrombophilia testing was performed if it could be done reliably. Since non-DNA thrombophilia testing is inaccurate during the acute phase of thrombosis and during anticoagulation, testing was delayed early in our experience. As large cohorts of thrombophilia patients were followed up, it has been observed that thrombophilia testing has little, if any, value in the management of these patients.[25] Therefore, thrombophilia evaluations were not requested in the late part of this study.

A limitation of this study is that it is retrospective with no control patients treated with anticoagulation alone. A number of our patients were referred after failed initial treatment with anticoagulation alone, or failed attempts at CDT. Therefore, the outcomes observed here may not represent those expected in a nonreferral practice.

The strengths of this study are that all patients with iliofemoral DVT who were treated with CDT are included in this analysis. All had pre- and post-treatment phlebography. Phlebographic evaluations were performed by physicians who were blinded to the clinical outcomes of patients, and physicians caring for patients were unaware of the details of lytic outcome.

This is the first report suggesting a direct relationship between the phlebographic degree of residual thrombus with recurrent DVT following CDT. It is our impression that there is a more linear correlation of recurrence with residual thrombus than reported here; however, much larger patient numbers will be required to demonstrate such a linear relationship. We found no correlates with recurrent thrombosis other than residual thrombus. Moreover, the diagnosis of recurrent DVT was made by physicians who were unaware of the success of CDT for patient's initial IFDVT. We are optimistic that as more information is gathered on the benefits of strategies of thrombus removal for patients with IFDVT, treatment designed to eliminate thrombus, restore patency and preserve valve function will be widely adapted. This should result in fewer recurrences, less post-thrombotic morbidit, and improved health-related quality of life.

An NIH-funded trial, ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis), is currently in progress, which is randomising patients with proximal DVT to anticoagulation alone or to CDT and anticoagulation.[26] Patients will be stratified at randomisation with

regard to the location of their thrombus, IFDVT or femoropopliteal DVT. ATTRACT will help answer the questions of whether CDT improves outcomes after DVT, reduces PTS, reduces recurrence and is cost-effective. However, in the absence of definitive data from randomised controlled trials, observational evidence suggests that CDT restores patency, preserves valve function and improves quality of life. Observations from this study now show that the risk of recurrent DVT is diminished following treatment with CDT and that risk of recurrence is related to residual thrombus.

Disclosure

Dr Comerota is a consultant for Covidien, Inc.

Acknowledgements

We are indebted to Marilyn Gravett, MFA, for expert assistance with the preparation of this manuscript, and to John Chen, PhD, for his assistance with statistical analysis. This study was supported in part by the Conrad and Caroline Jobst Foundation of Toledo, Ohio, USA.

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