Randomized study of different approaches for catheter-directed thrombolysis for lower-extremity acute deep venous thrombosis

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Received 20 December 2014; received in revised form 18 June 2015; accepted 1 July 2015

Background/Purpose: To investigate the feasibility, effectiveness, and complications of catheter-directed thrombolysis (CDT) using three different approaches for acute lower-extremity deep venous thrombosis (DVT).

Methods: A total of 106 patients with acute DVT were enrolled in this study. Forty-one patients received CDT through the small saphenous vein (Group A), 35 through the great saphenous vein (Group B), and 30 through the popliteal vein (Group C). Iliac vein balloon dilation and stenting was performed in 65 cases.

Results: The vascular approach route was not statistically related to limb edema reduction rates (Groups A, B, and C: 82.3 ± 7.6% vs. 81.6 ± 6.0% vs. 83.9 ± 6.1%), nor to thrombolysis rates (63.5 ± 7.7% vs. 66.9 ± 8.4% vs. 66.1 ± 2.7%). The procedure was significantly shorter for Groups B and C. No significant difference was found between Groups B and C. Most complications occurred in Group A. The complication rate in Group B was the lowest. Eighty-eight patients were followed up for 7–24 months. Of these, 78 were pain-free and without limb edema; six showed rethrombosis.

Conclusion: CDT is an effective method to manage acute DVT. Of the three routes tested, the small saphenous vein route was associated with more frequent complications. Great saphenous vein catheterization was more effective because of its lower complication rate.

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Introduction

Deep venous thrombosis (DVT) is commonly associated with vascular surgery, but there are very many other causes. Millions of patients are at risk of developing DVT, and it is estimated that > 250,000 new cases occur every year. Pulmonary embolus is the most serious complication of DVT, and > 50,000 patients die every year as a result of pulmonary embolus.\(^1\) Even when DVT is diagnosed expeditiously, many patients are inadequately treated and experience a 20–50% recurrence rate. Furthermore, ~30% of patients who develop DVT experience life-long post-thrombotic syndrome.\(^2\)

In addition to the acute risks of DVT, there are important long-term complications. Thrombus can cause valvar incompetence and luminal obstruction, which can ultimately lead to chronic deep venous insufficiency and chronic venous disease, such as chronic varicose ulceration, hyperpigmentation, pain, and edema, all of which represent a significant socioeconomic burden.\(^3\) The main long-term goal of treatment for DVT is to prevent chronic deep venous insufficiency. Therefore, although the patency of the thrombolysed vein is of relevance, the venous valve function may be at least as important.

Thrombolytic agents may be delivered by systemic infusion, local-regional administration, or catheter-directed therapy. Systemic administration is associated with long infusion times, a high incidence of partial thrombolysis, and a significant rate of bleeding complications. In catheter-directed thrombolytic therapy (CDT), the tip of the catheter is placed inside the thrombus and the thrombolytic agent is administered directly therein. It is hoped that CDT preserves venous valves, thus restoring flow in the deep venous system and minimizing the long-term complications of DVT.\(^4\) To date, the approaches for CDT reported in the literature include the right jugular vein, contralateral femoral vein, popliteal vein, great saphenous vein, and small saphenous vein. The popliteal vein is the choice in most procedures for catheterization; in our experience, however, this approach may not be possible in some patients. It is also important to review techniques to identify the safest and most effective approaches.

In this study, we reviewed the records of 106 patients admitted to our hospital with acute lower-extremity DVT who were treated with CDT using different access routes, including the small saphenous vein, great saphenous vein, and popliteal vein, between September 2011 and November 2013.

Methods

Ethics approval

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Soo Chow University, Suzhou, China (File No: 2011270).

Study groups

Between September 2011 and November 2013, 126 patients with extensive acute lower-extremity DVT were initially enrolled into this study and were randomized into three groups (Figure 1). Twenty patients were excluded from this study because of high blood pressure, thrombocytopenia, limb infection, or cardiac insufficiency, leaving 106 patients. Demographic information collected included age, sex, cause of DVT, duration of DVT before admission and which extremity was involved. Presenting symptoms included limb pain, phlegmasia, and edema. All patients were confirmed to have DVT by conventional venography before CDT, and only patients with extensive thrombosis including the femoropopliteal vein and iliac vein were recruited. All patients were randomly allocated to one of three groups. Randomization was determined sequentially, i.e., since the presentation of patients to the hospital is effectively random, procedures were allocated according to the previous allocation. Patient 1 received Procedure A, Patient 2 received Procedure B, Patient 3 received Procedure C, Patient 4 received Procedure A, etc. Groups A–C underwent catheterization via the small saphenous vein, the great saphenous vein and the popliteal vein, respectively. Of the 20 patients excluded from this study, there were one patient, seven patients, and 12 patients excluded from Groups A, B, and C, respectively. The group size was determined by the study duration, i.e. the study was planned to be carried out over 2 years, which meant that ~100 patients would be recruited during the period, based on previous experience of serious DVT incidence.

Prior to CDT, all patients were evaluated by the same member of the operation team to confirm their suitability for thrombolysis therapy. The inclusion criteria were: acute lower-extremity DVT (symptoms lasting < 14 days); extensive DVT (including iliac, femoral, and popliteal veins); age 15–75 years; thrombosis confirmed by anterograde venography using the dorsal vein; and informed signed consent by the patient to participate. The exclusion criteria were: contraindications to the use of anticoagulant drugs, thrombolytic drugs or intravenous contrast media; history of intracranial or internal hemorrhage in the previous 3 months; history of serious trauma or major operation in the preceding 4 weeks; pregnancy; high blood pressure (systolic blood pressure >180 mmHg, diastolic blood pressure >110 mmHg); and history of ipsilateral DVT.

Safety

For safety, the first procedure was to insert a retrievable filter into the inferior vena cava. If the temporary filter was free of thrombus, it was removed; otherwise, the filter was implanted permanently.

Catheter implantation

(1) Catheterization through the small saphenous vein: Patients were placed prone on the angiographic table, and a longitudinal incision of approximately 2 cm was made between the ipsilateral external malleolus and the Achilles tendon to expose the small saphenous vein. A 5F sheath was inserted, through which all subsequent catheter and wire exchanges were performed. Under the guidance of
an elbowed catheter, a hydrophilic guide wire was navigated through the small saphenous vein to the popliteal vein and to the IVC. Then, a multiple-side-hole 5F coaxial catheter (UniFuse; Angiodynamics, Queensbury, NY, USA) was exchanged. Using a 50-cm catheter, the tip was placed at the iliocaval junction.

(2) Catheterization through the great saphenous vein: Patients were placed in the same position as they would be placed for IVC filter insertion. After puncture, a 5F sheath was inserted into the great saphenous vein with the guidance of ultrasound, and a guidewire was inserted into the popliteal vein via communicating branches between the superficial and deep venous system, assisted by a road map resulting from venography performed via the sheath.

(3) Catheterization through the popliteal vein: With the patient prone on the angiographic table, the popliteal vein was accessed under ultrasonographic guidance with a small-gauge echogenic needle to avoid inadvertent puncture of the adjacent popliteal artery. A 5F sheath was inserted, and catheterization was performed as described previously for the small saphenous vein.

Thrombolysis

In all cases, thrombolysis was carried out using urokinase. Infusion was performed through the coaxial catheter at an even speed with a total dose of 10,000 units/kg/24 h. Low-molecular-weight heparin was administered systemically during the procedure and after lysis. Lysis progression was monitored with daily venography. Thrombolysis was terminated if no additional lysis was achieved in the preceding 24 hours or there was a fibrinogen level < 1.0 g/L. Thrombolysis was discontinued after 5–7 days. Laboratory tests, including hematocrit, prothrombin time, activated partial thromboplastin time, and international normalized ratio (INR), were determined before and after lysis and throughout the patient’s hospital stay.

Adjunctive treatment of iliac lesions

Self-expandable metallic stents (Bard Luminexx, 14 mm × 80 mm) were used to treat lesions that had been obscured by thrombus but were “uncovered” after thrombolysis, particularly stenoses and/or short occlusions at the level of the iliac veins. Some of these lesions may represent cases of May-Thurner syndrome, in which the left iliac vein is compressed by the right iliac artery. The diameter of the

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**Figure 1** CONSORT 2010 flow diagram.
percutaneous transluminal angioplasty balloon was selected to match the size of the vein adjacent to the lesion while the stent was measured to be 2 mm oversized, and the length to cover the stenotic segment was measured to include a 2-cm margin.

Post-thrombolysis therapy

Warfarin administration was routinely started prior to hospital discharge and was recommended to continue for at least 6 months. The INR target for post-thrombolysis therapy was 2.0–3.0. In addition, the patients were recommended to wear elastic stockings.

Evaluation

The percentage detumescence (ratio between pre- and postlysis thigh perimeter difference to prelysis thigh perimeter difference) was calculated. Circumferences were measured 20 cm above the knee.

\[
\text{% detumescence} = \frac{\text{Pretreatment thigh difference} - \text{post-treatment thigh difference}}{\text{Pretreatment thigh difference}} \times 100\% 
\]  

Venograms were reviewed, scored and graded for each infusion using a modification of the reporting standards for venous disease described by Porter and Moneta. A thrombus score was calculated for seven venous segments: the IVC, the common iliac vein, the external iliac vein, the common femoral vein, the proximal portion of the superficial femoral vein, the distal portion of the superficial femoral vein, and the popliteal vein. The thrombus score was 0 when the vein was patent and completely free of thrombus, 1 for partial occlusion, and 2 for complete occlusion. The total thrombus score before and after lysis was calculated by adding the scores of the seven venous segments before and after completion of treatment, which included lysis and any additional adjunctive procedures, such as stenting. The percentage of thrombolysis (the ratio of the difference between the pre- and postlysis scores with prelysis scores) was calculated.

Statistical analysis

All data were collected in a database (Access version 2; Microsoft) and analyzed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD) and compared by the F test, whereas categorical variables were analyzed by the Chi-square test. A \( p \) value < 0.05 was used as a threshold for statistical significance.

Follow-up

Symptomatic improvement and the overall mid-term thrombolytic patency rate assessed by venography at 6 months, 12 months, and 24 months through venography performed by the same operative team were recorded for all patients.

Results

Study patients

There were no deaths or symptomatic pulmonary embolisms among the patients in this study. The demographic data are presented in Table 1. DVT developed after abdominal or pelvic operations in 23 cases and after bone or joint operations in 21 cases. All operations had been performed at least 1 month before the patients underwent CDT. There were 15 cases of malignancy. The remainder were without obvious causes. Stenosis of common iliac veins with or without collateral circulation was found in 69 cases, according to the venograms taken during the CDT. Stenoses were all located at the iliocaval junction.

Treatment

Three retrievable filters were placed permanently because a residual thrombus was found below the filter by venography, including two of the filters in Group A and one in Group C. Adjunctive treatment with metallic stent placement was necessary to treat uncovered stenoses and/or short residual occlusions in 65 cases (24 cases in Group A, 22 cases in Group B, and 19 cases in Group C, respectively). Four patients refused iliac stenting, including two in Group A, one in Group B, and one in Group C. All procedures were performed in the left common iliac segments. There was no significant difference in the requirement for stenting between groups (A vs. B: \( \chi^2 = 0.148, p = 0.701 \); A vs. C: \( \chi^2 = 0.167, p = 0.683 \); and B vs. C: \( \chi^2 = 0.002, p = 0.968 \)).

Assessment of thrombolysis

There was no difference in the effectiveness of the procedure between the three groups according to the F-test. The time taken in Groups B and C was tested using the F-test and was significantly less than that in Group A (\( p = 0.007 \) and \( p = 0.013 \), respectively). No significant difference was found between Groups B and C (Table 2).

Complications

There were no major bleeding complications in the three groups. In Group A, minor bleeding events were recorded in four cases at the external ankle incisions, and the lowest concentration of fibrinogen was 0.3 g/L with a urokinase dose of 0.8 million IU/d. These four patients with minor
bleeding were treated with heparin saline (100 mg of heparin mixed with 500 mL of saline) at a rate of 2 mL/h for 24 hours to prevent thrombosis in the catheter. After bleeding ceased and the fibrinogen concentration recovered to > 1.0 g/L, the dose of urokinase was reduced to 8000 IU/kg/d. In one patient, phlebitis was recorded after catheterization. These symptoms disappeared after regional warm compress treatment with 50% salarmarum for 5 days without catheter removal. Peri-incisional anesthesia was recorded in two patients due to saphenous nerve injury during exposure of the small saphenous vein. In Group B, no complications were recorded. In Group C, swelling and pain were recorded in two patients at the puncture site after extubation. Hematoma fluid was confirmed by color ultrasound. These hematomas were self-absorbed at review 2 months later. The complication rate of Group B was lower than those of the other two groups (χ² = 6.404, p = 0.011 and χ² = 5.001, p = 0.025).

Follow-up

Eighteen patients were lost to follow-up because of lost contact. The remaining 88 patients (88/106) were followed up with venography; the median time post-CDT for the follow-up examination was 11.1 ± 1.3 months (range, 7–24 months). Seventy-eight patients had no symptoms (swelling, pain) at the follow-up, and five patients had mild edema, but their symptoms could be relieved by rest; in addition, there were five patients who had no symptom relief. Venography was used at follow-up, and complete patency was found in 70 patients with normal valve function. Partial patency was found in 12 patients, and rethrombosis was found in six patients. Four of the six cases of rethrombosis occurred within 2–3 months after CDT due to iliac vein stenoses without stent placement; whilst the other two rethrombosed at 3–5 months after CDT, probably due to premature cessation of warfarin therapy. The three filters were converted to the permanent type because a residual thrombus was found to be partially patent without IVC occlusion.

Discussion

CDT is an interventional thrombolysis method in which the tip of the catheter is placed inside the thrombus. Thus, the thrombolytic agent is administered directly into the thrombus. This method is considered to result in a higher rate of complete early opening of occluded veins than has been reported with systemic or local-regional administration of thrombolytic agents. The catheter used to treat this patient group was a coaxial catheter with a multiple side-hole system. The tip of the catheter is blocked by a steel-wire with a dilatation head during infusion, allowing urokinase to be sprayed through the side holes, delivering directed thrombolysis.

Venous access sites reported for thrombolysis have included the right jugular vein, contralateral common femoral vein, popliteal vein, and small saphenous vein. Antegrade approaches such as catheterization from the saphenous vein and popliteal vein are generally used and can reduce the resistance due to valves and reduce the risk of mechanical damage to valve leaflets caused by the catheter and guide wire during retrograde catheterization. A further advantage of antegrade catheterization is that chronic lesions are often encountered at the iliocaval junction, even in patients with acute DVT, which cannot

### Table 1 Patient demographics.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
<th>Mean age (y)</th>
<th>Limb</th>
<th>Duration, mean ± SD (range)</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>18</td>
<td>23</td>
<td></td>
<td>65 (28–73)</td>
<td>35</td>
<td>110 ± 70 h (12 h to 10 d)</td>
<td>Small saphenous vein</td>
</tr>
<tr>
<td>B</td>
<td>19</td>
<td>16</td>
<td></td>
<td>63 (28–70)</td>
<td>30</td>
<td>108 ± 67 h (10 h to 11 d)</td>
<td>Great saphenous vein</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>18</td>
<td></td>
<td>66 (21–71)</td>
<td>28</td>
<td>107 ± 66 h (11 h to 12 d)</td>
<td>Popliteal vein</td>
</tr>
</tbody>
</table>

SD = standard deviation.

### Table 2 Catheter-directed thrombolysis through three different approaches. a

<table>
<thead>
<tr>
<th>Group</th>
<th>TFC (min)</th>
<th>Clinical effect</th>
<th>PD (%)</th>
<th>Venography evaluation</th>
<th>PT (%)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prelysis</td>
<td>Postlysis</td>
<td></td>
<td>Prelysis Score</td>
<td>Postlysis Score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPD (cm)</td>
<td>TPD (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>13.5 ± 1.2</td>
<td>6.9 ± 2.1</td>
<td>1.2 ± 1.1</td>
<td>1.2 ± 1.1</td>
<td>82.3 ± 7.6a</td>
<td>9.0 ± 2.6</td>
</tr>
<tr>
<td>B</td>
<td>4.9 ± 0.2</td>
<td>5.8 ± 0.9</td>
<td>1.1 ± 0.7</td>
<td>1.1 ± 0.7</td>
<td>81.6 ± 6.0b</td>
<td>7.9 ± 2.2</td>
</tr>
<tr>
<td>C</td>
<td>5.6 ± 0.6</td>
<td>7.1 ± 1.9</td>
<td>1.3 ± 0.9</td>
<td>1.3 ± 0.9</td>
<td>83.9 ± 6.1c</td>
<td>8.5 ± 1.9</td>
</tr>
</tbody>
</table>

PD = percentage of detumescence; PT = percentage of thrombolysis; TFC = time taken for catheterization; TPD = thigh perimeter difference.

a “a” compared with “b”, p = 0.709; “a” compared with “c”, p = 0.523; “b” compared with “c”, p = 0.436; “d” compared with e, p = 0.060; d compared with f, p = 0.311; “e” compared with f, p = 0.803.
predictably be traversed with a cephalic approach from the right internal jugular vein or the contralateral femoral vein.

However, CDT through antegrade approaches such as the small saphenous vein or popliteal vein also has some disadvantages, such as patients needing to change from a dorsal to a prone position between filter placement and catheterization. We noted that some elderly patients and also those who had received lumbar spine or joint operations found it difficult to change position. Also, complications due to small saphenous vein exposure in a swollen limb may cause injury of the concomitant saphenous nerve. It was also important to avoid inadvertent puncture of the adjacent popliteal artery and nerve when the patient was randomized to the popliteal vein approach. This was a risk even under ultrasonographic guidance.9

Therefore, we felt the best approach might be the great saphenous vein, which we adopted for 35 patients. The great saphenous vein is initiated at the dorsal venous arch of the foot. It is superficial at the location of the internal malleolus. Thus, the operator could perform catheterization without incision or ultrasound guidance, and patients were not required to change position after IV filter placement. Punctures at this site have the benefits of a low bleeding complication rate and convenient nursing care. However, the great saphenous vein does not join the popliteal vein anatomically; therefore, a communicating branch between the ipsilateral great saphenous vein and popliteal vein must be identified by venography and catheterization must be performed under road map guidance. This procedure requires a tight tourniquet at the location below the knee to help reveal a suitable course.

The effect of lesions at the left common iliac vein on DVT have been extensively studied. It has been shown that it is not sufficient simply to remove the thrombus and leave the iliac lesion alone. In this study group, 69 patients out of 106 (65.1%) had a complicated left common iliac vein stenosis. These lesions were always located at the iliocaval junction, and the frequency was comparable to other reports.10 Li et al11 treated nonthrombosed iliac vein stenosis/occlusion with stent placement and reported a patency rate of 94.6% in a 3-year follow-up study. This result verified that metallic stents are safe for the treatment of iliac vein lesions. In addition, Hood and Alexander12 reported 99% complete early lysis have been consistently higher in several investigations using CDT therapy.13,14 The prevalence of post-thrombotic syndrome is also consistently lower than that with other forms of administration.14,15

In conclusion, CDT with iliac venous intervention is an effective method for the treatment of acute DVT. Choosing the great saphenous vein as an approach made this method easier, with fewer complications.

Acknowledgments

This research was supported by the Health Research Projects in Jiangsu Province, China (No: H201419).

References