Restoration of Patency in Iliofemoral Deep Vein Thrombosis with Catheter-Directed Thrombolysis Does Not Always Prevent Post-Thrombotic Damage


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KEYWORDS
Deep vein thrombosis; Thrombolysis; Catheter-directed thrombolysis

Abstract  Objectives: To evaluate the long-term results of catheter-directed thrombolysis (CDT) and the feasibility of stent placement for lower extremity deep vein thrombosis (DVT).
Design & methods: Retrospective study of 34 patients (10 men and 24 women, mean age 55, S.D. 13 years) with lower extremity DVT underwent CDT at Seoul National University Hospital from January 1999 to October 2003. Patient characteristics, risk factors of DVT, extent of thrombosis, and short-term and long-term results of CDT and/or stent placement were analysed.
Results: Mean follow-up times were 47 S.D. 16 months. The primary technical success rate was 97% (complete lysis 68%, partial 29%). During the follow-up periods 11 (32%) patients showed re-thrombosis. Sixteen (47%) of 34 patients showed chronic change of vessels during the follow-up periods. By Cox Proportional Hazard analysis, extent of thrombolysis was a statistically significant factor affecting the freedom of re-thrombosis and chronic change ($P = 0.008$ and $P = 0.001$). Nine (44%) of 21 deployed stents were obstructed, and the overall stent patency at 3 years was 56.7%. The only factor affecting the stent patency was stent length more than 6 cm ($P = 0.002$, HR 13, 95% CI 2.7–59).

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Introduction

Deep vein thrombosis (DVT) of lower extremity can lead to pulmonary embolism (PE) in the short term and post-thrombotic syndrome in the long term.\textsuperscript{1,2} Although the conventional treatment of acute DVT is systemic anticoagulation (heparinisation followed by oral anticoagulant with warfarin) to prevent PE and recurrent DVT, this form of therapy does not protect the patient from post-thrombotic syndrome, which can appear months to years after the acute episode of DVT. In addition, the results have been largely inadequate in terms of rapid resolution of symptoms, re-canalisation of long-segment venous occlusions, and long-term disability from chronic venous insufficiency.

Early thrombus removal is a logical approach to improve the long-term outcome of iliofemoral DVT. Treatment strategies include systemic thrombolytic therapy, surgical thrombectomy, and catheter-directed thrombolysis (CDT) with or without stent placement.\textsuperscript{3-5} CDT allows a higher concentration of the thrombolytic drug to be introduced directly into the clot. Regional thrombolysis results in more rapid dissolution of the thrombus and reduced haemorrhagic complications compared with systemic infusion.\textsuperscript{6}

Although the short-term results of CDT for lower extremity DVT have been favourable, there are few reports regarding the long-term benefits. The aim of this study is to evaluate the long-term results of CDT and the feasibility of stent placement for lower extremity DVT.

Materials and Methods

Patients

Medical records of all patients who underwent catheter-directed thrombolysis (CDT) and/or stent placement for lower extremity DVT were reviewed. Between January 1999 and October 2003, 34 consecutive patients with 35 symptomatic limbs were identified. All patients underwent duplex scan and/or computed venography for diagnosis, treatment, and follow-up for a mean of 47 S.D. 16 months.

The patients included 10 male and 24 female patients, with a mean age of 55 S.D. 13 years. Acute (≤14 days) DVT was treated in 30 limbs and chronic (>28 days) DVT in 2 patients (mean duration, 9 S.D. 17 days; median, 3.5 days; range, 1–90 days). The treated extremity was on the left side in 26 of 35 limbs (74%), on the right in 7 (20%), and both in one patient (3%). One patient had lower extremity DVT in both limbs, but CDT was performed on the left side at acute onset. All patients had iliofemoral DVT with or without distal involvement, and extension to distal inferior vena cava (IVC) was found in 6 cases (Table 1). The risk factors of DVT were May–Thurner syndrome in 14 (41%) of 34 patients, hypercoagulability in 11, immobilisation in 3, vascular compression by intra-abdominal mass in 3, vascular injury in 3, and unknown origin chronic stenosis of common iliac vein in 4. No patient had previous history of DVT or oral contraceptive pill medication.

Procedures

The institutional review board approved this retrospective investigation, and informed consent was obtained from each patient after a discussion of the risks and benefits of use of urokinase for CDT, the surgical treatment alternatives including thrombectomy, and the standard medical therapy.

Vascular access into the affected limb was achieved through ultrasound (US)-guided entry into the ipsilateral popliteal vein in all cases. A 6-F vascular sheath was typically inserted, through which all subsequent catheter and wire exchanges were performed. Urokinase was the thrombolytic drug used to treat all cases and infusion was performed using a multiple-side-hole system. The starting and ending times of thrombolysis, as well as the concentration and total amount of urokinase administered, were recorded. All patients received sub-therapeutic heparin (300–500 U/h) through the vascular sheath during the procedure. The partial thromboplastin time, haematocrit, and fibrinogen level were monitored. Prophylactic IVC filter
Placement was selectively performed in case of floating thrombus in the vena cava performed.

If residual organised thrombus and/or stenotic segment was found in follow-up venography, balloon angioplasty (n = 27, 79%), aspiration thrombectomy (n = 4), and self-expandable Nitinol stent placement (n = 21, 62%) were performed. After establishment of venous patency, all the patients were treated with intravenous hydration, compression stockings (30–40 mmHg ankle gradient stockings) and were encouraged to ambulate the ward. In addition, patients were treated with the anticoagulant, heparin (unfractionated or low molecular weight heparin) and converted to oral warfarin for a minimum of 6 months (mean 23 S.D. 17 months, range, 6–72). The target therapeutic range for the international normalized ratio (INR) was 2–3 in most patients. V/Q scan was also performed to rule out PE in 19 patients before CDT, 18 after CDT and 12 before and after CDT.

Technical and clinical success evaluation and follow-up

The degree of thrombolysis was calculated on the venogram obtained after completion of treatment, including lysis and additional adjunctive procedure, but before stent deployment, used to treat lesions uncovered after thrombolysis. Using the modified SVS scoring system, clot burden for each vessel was scored from zero to three. In brief, a vessel score of zero indicated a patent vein. A vessel score of one indicated a segmental non-occlusive thrombus was present. A vessel score of two indicated a segmental, occlusive thrombus was present, and a vessel score of three indicated an occlusive thrombus in the entire length of the vessel segment. Each vessel (vena cava, iliac, common femoral, femoral, popliteal, and calf) was individually scored and then added together to generate the clot burden for the entire limb. The clot burden reduction was calculated as the difference between pre- and post-CDT limb scores, then divided by the pre-CDT score, and then multiplied by 100%. Minimal or no thrombolysis was defined as grade I, <50% removal of pre-CDT clot burden, partial thrombolysis as grade II, 50–95%, and complete lysis as grade III, 95–100% removal.

Technical success was assessed from the final venogram of each treated limb and was defined as successful restoration of venous patency. Clinical success was assessed in each treated limb and was defined as the presence of technical success in conjunction with considerable improvement in lower extremity swelling and/or pain. 

Computed tomographic venography or duplex scan was performed at 1, 3, 6 and 12 months after lysis, and then at 12-month intervals to evaluate the patency of the treated venous segment and/or that of the stent. The earliest date that any of the six lower extremity vessel segments originally treated by CDT demonstrated thrombosis was defined as the re-thrombosis date. Chronic change of vessels was defined as luminal narrowing or cord-like fibrotic change of the corresponding vessel segments demonstrated in subsequent computed venography. The suspicious patients among them were submitted to undergo duplex scan for the confirmation of venous insufficiency. In addition, patients were evaluated for the clinical occurrence of oedema, pigmentation, development of varices, and ulceration on the treated limb.

Statistical analysis

All non-parametric values are presented as mean and S.D. The Chi-square or the Fisher’s exact test for comparison of categorical variables and Student’s t-test for continuous variables were used to test statistical significance. The patency rate of iliofemoral vein and stenting was analysed by Kaplan–Meier method and Cox’s proportional hazards model. SPSS release 12.0 (SPCC Inc.) was used, and differences were considered statistically significant at P < 0.05 (two-tailed).

Results

Degree of thrombolysis

The mean duration of thrombolysis was 28 S.D. 12 h and mean total amount of urokinase was 2.6 S.D. 1.2 million IU per treated limb. Pre- and post-CDT clot burden is described in Table 1. The overall limb score decreased from an average 10.4, pre-CDT, to an average 1.1, post-CDT. The mean clot burden reduction was 88% after CDT. Complete lysis was achieved in 18 (53%) of 34 patients, partial lysis was achieved in 14 (41%) of 34 patients and the technical success rate was 97%. There was no difference in the duration of thrombolysis therapy between complete and partial lysis. The mean duration was 26 S.D 12 and 29 S.D 13 h in each group. No response to thrombolysis was observed in one patient (3%). This patient had chronic DVT and received CDT for 90 h with balloon dilatation and stent placement that failed. Therefore she underwent surgical thrombectomy and patch-angioplasty. The 27-year-old female patient had the venous anomaly of duplicated popliteal vein (PV) and had multiple segmental partial thrombosis in CFV, SFV, and medial side PV. After CDT, there was a small amount of residual thrombus in CFV; however the treatment with thrombectomy and patch angioplasty ultimately failed. As a whole, statistically significant clot burden reduction was achieved in all six vessel segments (Table 1).

In 21 limbs, adjunctive treatment with metallic stent placement was necessary to treat stenoses and/or short residual occlusions that were resistant to lytic treatment; 14 of these procedures were performed in patients with May–Thurner syndrome. A self-expandable Nitinol stent was used in all cases; the mean diameter and the length of the stent were 13 S.D. 1.4 mm and 5.4 S.D. 1.6 cm, respectively.

Complications

Bleeding complications developed in 2 (6%) of 34 patients. In both cases, unexpected vaginal bleeding was observed. One case with minor bleeding was treated successfully with conservative management, and the other case showed major bleeding which required transfusion of 6 units of packed RBC.

V/Q scan showed high or intermediate probability of pulmonary embolism in 3 of 12 patients before and after
CDT; however, no patients experienced aggravation of symptoms or signs of pulmonary embolism, even after the stent placement in May–Thurner syndrome. No immediate deaths were reported as a result of CDT.

Clinical follow-up and long-term patency

Long-term clinical follow-up was available for all patients for a mean duration of 47 S.D. 16 months (median, 45 months, range, 15–85 months) post procedure. Mean duration of anticoagulation was 23 S.D. 17 months (range, 6–72 months). In the follow-up period, symptomatic recurrences were detected in 13 of 34 patients. Among these patients, post-thrombotic syndrome was observed in 7 patients (21%) and re-thrombosis in 11 (32%), including 5 (15%) patients who underwent re-thrombolysis for recurrent lesions, but showed partial lysis finally resulting in chronic post-thrombotic damage and stenosis. Freedom from re-thrombosis by Kaplan–Meier analysis at 1, 2, and 3 years is 74%, 71%, and 67%, respectively. By Cox Proportional Hazard analysis, post-CDT residual thrombosis in iliac vein increased the re-thrombosis rate (Fig. 1, P = 0.008, RR 5.3, CI 1.5–18).

Sixteen (47%) of 34 patients showed chronic changes of vessels during the mean 42 S.D. 20 month follow-up, and the freedom from chronic change by Kaplan–Meier analysis at 1, 3, and 5 years is 88%, 73%, and 45%, respectively (Fig. 3). Among the 18 patients who achieved complete lysis, 5 patients had recurring DVT and 13 patients did not. All of the 5 patients experienced chronic changes of vessels in the end, but only one patient without recurrent DVT showed a chronic change (P = 0.001) By Cox Proportional

Figure 1 Freedom from re-thrombosis. Eleven (32%) of 34 patients showed re-thrombosis during follow-up, and the freedom from re-thrombosis by Kaplan–Meier analysis at 1, 2, and 3 years is 74%, 71%, and 67%, respectively. Residual thrombus in iliac vein after CDT was risk factor of re-thrombosis. By Cox Proportional Hazard analysis, post-CDT residual thrombosis in iliac vein increased the re-thrombosis rate (RR 5.3, CI 1.5–18, P = 0.008).

Figure 2 Freedom from chronic change of vessel after CDT. Sixteen (47%) of 34 patients showed chronic changes of vessels, and the freedom from chronic change by Kaplan–Meier analysis at 1, 3, and 5 years is 88%, 73%, and 45%, respectively. By Cox Proportional Hazard analysis, re-thrombosis after CDT increased the chronic change rate (RR 7.6, CI 2.4–24, P = 0.001).

Hazard analysis, re-thrombosis increased the chronic change rate (Fig. 2, P = 0.001, RR 7.6, CI 2.4–24).

Regarding stent placement in the long term, freedom from re-thrombosis or chronic change was likely to be lower in the stent group than in the no-stent group, but this not statistically significant. Nine (44%) of 21 deployed stents were obstructed within the mean 31 S.D. 22 month

Figure 3 The patency of stent. Nine (43.8%) of 21 deployed stents were obstructed, and the overall stent patency at 3 years was 57%. In multivariate analysis, the only factor affecting the stent patency was stent length more than 6 cm (P = 0.002, HR 13, 95% CI 2.7–59).
follow-up, and the overall stent patency at 3 years was 57%. Among the risk factors for stent obstruction shown in Table 2, residual thrombosis, stent length more than 6 cm, and re-lysis were significant statistically. In multivariate analysis, the only factor affecting the stent patency was stent length more than 6 cm (Fig. 3, \( P = 0.002, \text{HR} 13, 95\% \text{CI} 2.7–59\)).

Two patients died during the follow-up period of more than 2 years; the causes of death were not directly related to CDT procedures or complications (advanced gastric cancer and hepatocellular carcinoma), but these patients were included in the statistical analysis.

Discussion

The therapeutic goals for treating patients with acute DVT include prevention of PE, restoration of unobstructed blood flow through the thrombosed segment, prevention of recurrent thrombosis, and preservation of venous valve function. Successful achievement of these clinical goals will minimise the morbidity and mortality of PE and will diminish the sequelae of post-thrombotic syndrome. Up to two-thirds of patients with iliofemoral DVT will develop oedema and pain, and 5% will develop ulcers despite adequate anticoagulation.5,10

Thrombolysis is a potentially attractive form of therapy because it provides the opportunity for prompt restoration of venous patency and preservation of venous valve function. The report by Semb and Dake4 in 1994 provided early insight into the potential role of catheter-directed thrombolytic techniques. By focusing the delivery of higher concentrations of thrombolytic agents, lysis rates can be improved, treatment duration can be reduced, and complications associated with patient exposure to systemic thrombolytic therapy may be reduced. Furthermore, defects such as stenosis of the common iliac vein can be treated by balloon angioplasty with or without the placement of endovascular stents.

The initial technical success rate of CDT is reported to be as high as 78–95%,5,7,11 and our study showed a similar success rate of 97%. According to many literature reviews, the primary patency rate of DVT at 1 year after CDT is 50–95%, which declines for the initial 6–12 months. Even after 12 months, DVT recurrence can be observed, therefore it is not adequate to evaluate the 1 year patency rate of CDT.5,7

Our results showed that the patency rate of DVT was likely to decline for the initial 24 months after CDT and to be maintained thereafter. Thus, it would be reasonable to evaluate the patency rate of CDT a minimum of 24 months after the procedure.

The known risk factors associated with DVT recurrence are hypercoagulability, extent and age of thrombosis, previous history of DVT, malignancy, early withdrawal of anticoagulation, Behcet’s disease, anatomic abnormality of lower extremity, and residual thrombus resulting from incomplete lysis. In our study, 11 of 34 patients showed laboratory hypercoagulability, including 4 patients with complex coagulation factor abnormalities, protein C deficiency in 4, protein 5 deficiency in 7, antithrombin (AT) III deficiency in 1, and hypoplasmigenaemia in 1. Eight (73%) of 11 patients with coagulation abnormality experienced DVT recurrence and/or chronic DVT, and the patency rate was statistically significantly lowered (\( P = 0.03 \)). In patients with hypercoagulability, intravenous heparinisation and prolonged anticoagulation with warfarin is mandatory in cases of trauma or surgery, but delivery increases the risk of thrombosis.12 In addition, they tend to experience DVT before the age of 40 years, so DVT developed at a young age requires thorough evaluation for hypercoagulability and should be treated with prolonged anticoagulation therapy. Similar to other reports, other significant risk factors of DVT recurrence included initial incomplete thrombolysis (\( P = 0.030 \)) and extent of DVT (\( P = 0.026 \)). However, in a Cox Proportional Hazard analysis, residual thrombosis in iliac vein after CDT was the only risk factor increasing the likelihood of re-thrombosis (\( P = 0.008 \)).

After thrombolysis, the degree of lysis was a significant predictor of early and continued patency. At 3 years, 75% of limbs with complete thrombolysis remained patent, as compared with 30% of limbs with partial lysis (\( P = 0.03 \)). In general, acute DVT was a predictor of a better lysis grade than chronic DVT, although substantial lysis could be achieved in patients with chronic iliofemoral DVT. In this study, the critical time was less than 5 days from onset to intervention, which was a shorter time period than the 14 days reported previously.11 However, two of three patients treated more than 14 days from symptom onset showed long-term patency, and it may be beneficial to try CDT in these patients. On the basis of these data, CDT should be offered to patients with acute onset DVT with no previous history of DVT in whom complete lysis can be anticipated.

In general, adjunctive metallic stent placement after CDT has a patency rate of 64–95%.11,13 Vedantham et al., who reported 93% mid-term stent patency in 15 patients, suggested that early stent placement would minimise the dosage and the systemic side effects of thrombolytic drugs and yield a higher patency rate.3 However, instability of the metallic stent and no available reports of long-term results were limitations of their study. In our study of the long-term results of stent placement after CDT, there was no difference in the freedom of re-thrombosis nor chronic change between stent and no-stent groups (\( P = 0.643 \)), possibly due to selection bias. We inserted stents in all cases of May—Thurner syndrome, in which stent placement could reduce the risk of DVT recurrence. In patients with hypercoagulability and venous compression due to intra-abdominal mass, the beneficial effects of a stent are not

**Table 2** Factors affecting the stent patency (univariate analysis, \( n = 21 \))

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<thead>
<tr>
<th>Variables</th>
<th>Criteria</th>
<th>( P )-value</th>
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<tr>
<td>Age (years old)</td>
<td>(&lt; 40 \text{ vs. } &gt; 40 ) NS</td>
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<tr>
<td>Gender</td>
<td>NS</td>
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<tr>
<td>Age of thrombus (days)</td>
<td>(&lt; 14 \text{ vs. } &gt; 14 ) NS</td>
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<tr>
<td>Hypercoagulability</td>
<td>NS</td>
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<tr>
<td>Extent of thrombus</td>
<td>Involvement below femoral artery NS</td>
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<tr>
<td>Degree of thrombolysis</td>
<td>Complete vs. partial 0.008</td>
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<tr>
<td>Stent length (cm)</td>
<td>(&lt; 6 \text{ vs. } &gt; 6 ) 0.008</td>
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<tr>
<td>Re-thrombolysis</td>
<td>0.008</td>
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*In multivariate analysis, \( P = 0.002 (RR 13, 95\% \text{CI} 2.7–59) \).
distinct and they do not show statistical significance. Unlike other reports, as a result of patient selection bias, the stent placement group was not likely to have a higher patency rate than the no-stent group.

Our study also revealed the risk factors associated with the long-term patency of the stent itself, such as incomplete thrombolysis ($P = 0.008$), re-lysis ($P = 0.008$) and stent length longer than 6 cm ($P = 0.008$). Among these, long stent placement was the only significant factor in a multivariate analysis and we consider that this should be avoided if possible. Although there have been no other reports about the effect of stent length on patency after CDT, it is reported in coronary interventions that a longer stent promotes platelet activation and increases re-stenosis.14,15

Sixteen of 34 patients developed post-thrombotic scarring of deep veins during the mean 42 month follow-up period. CDT is effective in early removal of clot burden and in restoration of venous flow, but cannot prevent subsequent deterioration of veins. In contrast, chronic change of vessel showed an initial slow decline, but after 2 years showed rapid progression despite of prolonged anticoagulation. Thus, it is suggested that careful long-term surveillance of the venous function is highly recommended after CDT.

Major bleeding complications were limited to two cases of vaginal bleeding in this series, which ceased with conservative management. In addition, although V/Q scan showed several cases of suspicious PE, there was no episode of symptomatic PE. Within the limitations of this small-sized retrospective study, information regarding valvular dysfunction and post-thrombotic syndrome could not be collected, suggesting a need for a further prospective study on a larger scale.

In conclusion, although the initial success rate of CDT was satisfactory, in long-term follow-up CDT resulted in a high frequency of recurrent DVT, especially in patients with residual thrombus after initial lysis, hypercoagulability, and longer extent of thrombus. Adjunctive self-expandable metallic stents have a beneficial effect in cases of iliac vein compression, stenosis due to organised thrombus, and focal obstruction, but a further prospective well-controlled study is needed to explore the long-term results. Long-term anticoagulation does not guarantee the maintenance of long-term patency. Initial patency was able to be maintained by the help of CDT. However, it was not effective in prevention of chronic change of the vessels in almost all cases, and careful long-term surveillance of the venous function is highly recommended after CDT.

Conflict of interest

None declared.

References