Pulse-spray Pharmacomechanical Thrombolysis for Proximal Deep Vein Thrombosis


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Objective. The aim of this study was to evaluate the efficacy, safety, and feasibility of pulse-spray pharmacomechanical thrombolysis to treat proximal deep vein thrombosis (DVT) in conjunction with the placement of a non-permanent IVC filter.

Methods. We studied 31 consecutive patients with acute proximal DVT defined as the inferior vena cava (IVC), iliac vein and/or femoral vein, who were diagnosed using duplex ultrasonography and/or contrast venography. All were treated with pulse-spray urokinase. Early success was assessed by comparing the pre- and post-treatment venographic severity score. Non-permanent IVC filters were used to reduce the risk of pulmonary thromboembolism.

Results. The average total urokinase dose was 1.71 million IU (range: 0.72–3.6 million IU) and the average duration of therapy was 2.4 days. The average percentage of thrombus lysed was 85% (range: 22–100%). A large thrombus trapped by the filter was detected using cavography before extraction of the filter in one patient. There was no major treatment-related adverse event.

Conclusion. The combination of pulse-spray pharmacomechanical thrombolysis and the prophylactic use of a non-permanent IVC filter was a safe and effective approach for treating acute proximal DVT.

Keywords: Deep vein thrombosis; Clinical trials; Fibrinolytic therapy; Intravascular devices; Pulmonary embolism.

Introduction

Deep vein thrombosis (DVT) can cause both pulmonary thromboembolism (PTE) and post-thrombotic syndrome. DVT treatment aims to relieve the acute symptoms of limb swelling and pain, reduce the risk of PTE, and prevent long-term disability from chronic venous insufficiency including persistent limb pain and swelling, hyperpigmentation, venous claudication, and skin ulceration. Early thrombolysis seems to be important to preserve valvular function.1,2 However, conventional treatment strategies, including anticoagulation and systemic thrombolytic therapy, do not lead to rapid resolution of proximal DVT. It has been reported that only 6% of patients treated with standard heparin anticoagulation alone for DVT of a lower extremity achieve clot lysis within 10 days of treatment,3 and thrombus propagation is seen in up to 40% despite adequate anticoagulation.4 Systemic thrombolysis is more effective than heparinization,5 but seems less effective than catheter-directed thrombolysis probably because of poor penetration of thrombi by the drugs which have been used.6 A recent report found that venous valvular function was better preserved in patients with iliofemoral DVT treated with catheter-directed thrombolysis than systemic thrombolysis.7 Although catheter-directed thrombolysis can be effective,8–21 the high daily dose of thrombolytic drug increases the risk of haemorrhage and can cause serious bleeding complications.22

Pulse-spray pharmacomechanical thrombolysis in which a highly concentrated fibrinolytic agent is injected directly into the thrombus as a brief high-pressure spray via multiple side hole ports in the catheter, has been used primarily to treat peripheral arterial occlusions.23–25 Pulse-spray pharmacomechanical thrombolysis for DVT appears superior to conventional catheter infusion thrombolysis in fragmenting and lysing the clot,23–25 but only a few case reports have been published.26–28 The routine use of an inferior vena cava (IVC) filter was not recommended for conventional catheter infusion thrombolysis for

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proximal DVT except for patients with poor cardiovascular reserve or patients with large, free-floating thrombi in the IVC. However, a non-permanent IVC filter was used before pulse-spray pharmacomechanical thrombolysis in this study because of the potential risk of pulmonary thromboembolism due to fragmentation of thrombi.

The combination of pulse-spray pharmacomechanical thrombolysis and non-permanent IVC filter placement should theoretically maximize the likelihood of successful thrombolysis while minimizing the risk of PTE and bleeding complications. The purpose of this study was to evaluate the efficacy, safety and feasibility of pulse-spray pharmacomechanical thrombolysis in conjunction with the placement of a non-permanent IVC filter for treating proximal DVT.

Patients and Methods

Between June 2002 and June 2004, patients were enrolled when they fulfilled the following three inclusion criteria: (1) DVT confirmed using duplex ultrasonography and/or contrast venography, (2) thrombus observed in proximal veins, including IVC, iliac vein, and femoral vein, and (3) clinical symptoms (duration of ≤30 days) such as swelling and pain. Exclusion criteria were: (1) Limb ischemia, (2) previous DVT of the ipsilateral limb, (3) contraindications to contrast media, anticoagulation, or thrombolytic agents, and (4) refusal of the treatment by the patient. After duplex ultrasonography, enhanced computed tomography and/or contrast ascending venography were performed to evaluate the extent of the thrombus. Lung scan, multidetector computed tomography and/or pulmonary angiography was performed to establish the presence or absence of pulmonary embolism before the procedure. Non-permanent IVC filters (Neuhaus Protect filter (Neuhaus Laboratories Inc., Miami, FL, USA), Antheor filter (Boston Scientific Corp., Natick, MA, USA) and Günther tulip filter (William Cook Europe, Bjaeverskov, Denmark)) were used. In cases of DVT involving the femoral vein, the catheter was always inserted through a popliteal vein in the supine position with the knee slightly flexed, and the leg rotated. In cases of DVT limited to the IVC and iliac vein, the catheter was inserted through the ipsilateral femoral vein.

Pharmacomechanical thrombolysis was performed using a Fountain infusion catheter (Merit Medical Systems Inc., South Jordan, UT, USA) with 80–320 side holes at 1.25 mm intervals in a spiral pattern. A penetrating spray was emitted from the side holes by manual injection. The catheter was positioned with the aid of a guidewire so that the side holes contacted most of the thrombus; the most proximal side hole was placed at the proximal edge of the thrombus. The guidewire was exchanged for a tip-occluding wire, which was inserted to close the end hole of the catheter, and the catheter was connected with a Y-shaped adaptor to facilitate drug injections around the wire.

The urokinase dose was 720,000 IU/day. The thrombolytic solution was prepared by dissolving 240,000 IU of urokinase in 50 ml of saline, and 240,000 IU per injection was administered three times a day. To maximize penetration into the thrombus, approximately 50 forceful and rapid manual pulse injections of 0.5- to 1.0-ml with the Squirt fluid dispensing system (Merit Medical Systems Inc., South Jordan, UT, USA) were administered manually about every 10 s. Progress was assessed at 1 or 2 day intervals by venography through the catheter (Fig. 1). Thrombolytic therapy was terminated when recanalisation and brisk venous flow was obtained or no progress was observed.

All patients received concomitant continuously infused heparin during the procedure through the catheter or the side port of the introducer sheath. The heparin dose was adjusted to control the activated partial thromboplastin time twice the control value. After the procedure, heparin was continued until therapeutic anticoagulation with warfarin was achieved.

The extent of clot lysis was assessed using a scoring system based on pre- and post-treatment venography. All venographic images were read and the score was calculated independently by two trained observers blinded to the clinical data. As we considered that venous recanalisation is effective for early symptom relief such as limb pain and swelling, an original scoring system was adopted in this study to discriminate occluded segments from non-occluded segments post-treatment. The score was calculated for nine venous segments of the upper, middle and lower IVC; the common iliac vein; the external iliac vein; the common femoral vein; the proximal and distal portions of the femoral vein, and the popliteal vein. The score was classified into seven categories according to the extent and form of thrombus: 0: No thrombus, 1: Thrombus extended over 1/3 of the length of the venous segment without occlusion, 2: Thrombus extended over 2/3 of the length of the venous segment without occlusion, 3: Thrombus extending along the entire length of the venous segment without occlusion, 4: Thrombus extending over 1/3 of the length of the venous segment with...
occlusion, 5: Thrombus extending over 2/3 of the length of the venous segment with occlusion, 6: Thrombus extending the entire length of the venous segment with occlusion. The total scores before and after treatment were then calculated by adding the scores of the nine venous segments. The difference between the pre- and post-treatment scores divided by the pre-treatment score and multiplied by 100 was classified as the percentage of thrombolysis achieved. After thrombolysis, further intervention consisting of balloon angioplasty or stent implantation was performed if there was an underlying significant venous stenosis. The post-treatment venographic severity score was calculated before additional adjunctive intervention. After the cavogram was obtained, the filter was extracted unless a definitive trapped clot was detected. If a trapped clot was demonstrated, the filter was extracted after the clot was dissolved by systemic thrombolysis.

The Ethics Committee of Mie University Hospital approved the study, and written informed consent was obtained from each enrolled patient.

Results

We recruited 31 patients (15 men and 16 women, mean age, 56 years, range: 19–81 years). Eleven patients were excluded from this study because of prior DVT of the ipsilateral limb in six patients and contraindication of thrombolytic therapy in five patients. The location of the thrombus and the treatment details are summarized in Tables 1 and 2. The median duration from onset to treatment was 9 days (range: 2–29 days). Left limbs were more frequently involved than right limbs (24 vs. 7). All patients had proximal DVT including thrombosis in the IVC, iliac and/or femoral vein. Before treatment, 18 patients had PTE detected.
through a lung scan, multidetector computed tomography and/or pulmonary angiography. The most favoured access site for the catheter was the ipsilateral popliteal vein. Successful placement of the thrombolysis catheter across the occluded vein was obtained in all cases. All patients received urokinase as the thrombolytic agent. The average total urokinase dose was 1.71 million IU (range; 0.72–3.60 million IU) and the average duration of therapy was 2.4 days (range: 1–5 days). The maximum length of the side hole portion of the catheter used in this study was 40 cm. If the length of the side hole portion was shorter than that of the occluded venous thrombus to be treated, the catheter was withdrawn to treat the remaining occluded region after initial treatment. An increased treatment duration of more than 3 days was necessary for patients with a long venous occluded lesion.

The average lytic rate, the percentage of thrombus in which thrombolysis was achieved, was 85% (range: 22–100%) (Fig. 2). A suboptimal lysis rate of less than 50% was recognized in one patient (3.2%) with residual organized thrombus secondary to iliac compression syndrome. Acute venous reocclusion occurred in a patient with advanced lung cancer at 2 weeks after treatment. No filter migration was observed during implantation period. In one patient, a large thrombus trapped by the filter was detected through cavography before extraction of the filter (Fig. 3). This patient was treated with the systemic administration of additional urokinase of 480,000 IU/day for 4 days. The non-permanent IVC filter was extracted after recognition of clot lysis through follow-up cavography. Moreover, although cavography could not definitely detect any trapped thrombus on the filter, a small thrombus was attached to the filter in 18 patients. No patients experienced symptomatic or fatal PTE. There were no major treatment-related adverse events, but one minor event: One patient experienced a small hematoma at the puncture site of catheter insertion. After pulse-spray thrombolysis, additional interventions were performed successfully for eight patients with residual venous stenoses resistant to thrombolysis; balloon angioplasty in eight patients and self-expandable metallic stent (Wallstent; Schneider, Minneapolis, USA) implantation for the common iliac vein in five patients (Fig. 4).

![Fig. 2. Venographic severity score before and after pulse-spray pharmacomechanical thrombolysis (error bars: Mean and standard deviation. *p < 0.0001 (paired t-test)).](image_url)
Fig. 3. Cavogram 2 days after pulse-spray pharmacomechanical thrombolysis showed thrombus trapped by the filter (left: Frontal image, right: Lateral image).

Fig. 4. Pre-treatment venogram showing abrupt and complete occlusion of left common femoral and iliac veins with poor collateral flow (A). Contrast media injected through the pulse-spray catheter penetrated the obstructing thrombus (B). Brisk flow was restored in the common femoral and iliac veins after pulse-spray pharmacomechanical thrombolysis, but significant residual stenosis of the left common iliac vein was demonstrated (C). After percutaneous balloon venoplasty (D), a wall stent was inserted in the left common iliac vein (E).
In our limited follow-up study, ascending venography ($n=21$) or enhanced multidetector computed tomography ($n=3$) was performed in 24 of 31 limbs at a mean post-treatment period of 11.1 months (range: 3–24 months), showing continued patency of the treated veins in 22 of 24 (91.7%). Objective clinical signs of post-thrombotic syndrome such as limb swelling, hyperpigmentation, chronic eczema and skin ulceration were evaluated in 30 of 31 limbs at a mean post-treatment period of 23.1 months (range: 13–37 months). Only one patient showed affected limb swelling as post-thrombotic syndrome 24 months after the procedure. Duplex ultrasound scanning with 6 MHz linear array transducer was performed to assess the venous reflux in 24 of 31 limbs at a mean post-treatment period of 25.1 months (range: 13–37 months). The patients were studied in the standing position. An automatic cuff inflator was used to induce the venous reflux with a maximum pressure of 80 mmHg for rapid inflation and deflation cuffs placed on the calf. Venous segments including the common femoral vein, femoral vein below the confluence with the profunda vein, popliteal vein and proximal great saphenous vein were evaluated. Cut-off values for the duration of reflux were defined as more than 1000 ms for common femoral vein, femoral vein and popliteal vein and more than 500 ms for great saphenous vein.29 Significant reflux was observed in three patients; the durations of reflux were 1280 ms at common femoral vein and 1260 ms at popliteal vein in one patient with affected limb swelling, 3700 ms at popliteal vein and 1260 ms at common femoral vein, respectively, in two patients without leg symptoms.

**Discussion**

Pulse-spray pharmacomechanical thrombolysis consists of brief high-pressure pulsed injections of a concentrated fibrinolytic agent throughout the clot via a multi-side-hole catheter. This method is expected to have the following advantages:24,25 (1) Macerating the clot and increasing the contact area of the thrombus with the thrombotic agent by penetrating intra-thrombic injections, (2) increasing the rate of lysis by applying the concentrated agent, (3) minimizing the dilution of the thrombolytic agent, systemic effects and effect of plasmin inhibitors in plasma owing to retention of the thrombolytic agent in the thrombus, (4) increasing the rate of lysis by simultaneous treatment of the entire thrombus, and (5) reduction of the cost and potential bleeding problems associated with the use of thrombolytic agents. Bookstein et al. describe the original technique of pulse-spray pharmacomechanical thrombolysis for the treatment of dialysis graft and arterial bypass graft occlusion.25 For graft occlusion, it has been reported that the pulse-spray method appears more effective than the conventional selective infusion method of catheter-directed thrombolysis.24,30–32 In an experimental study with animal models, the pulse-spray method was shown to be more effective than the conventional infusion method.23 It appears that the increased clot surface caused by maceration using the pulse-spray method is the main contributor to improvement of the rate of thrombolysis in patients with occluded grafts. For patients with proximal DVT, this pulse-spray method is also expected to be more effective than catheter-directed infusion thrombolysis because of the macerating effect by emitting fluids. To our knowledge, only a few case reports on pulse-spray pharmacomechanical thrombolysis for DVT have been published,26–28 although more than 10 reports of catheter-directed infusion thrombolysis for DVT have recently been published.8–21

Pulse-spray pharmacomechanical thrombolysis is especially advantageous in patients with completely occluded venous thrombosis. Thery et al., in a prospective study of 174 patients with proximal extensive DVT, reported that the thrombus is completely lysed with systemic infusion therapy of streptokinase in 60% of patients with non-occlusive clots compared with 14% among those with complete occlusion.33 Systemic thrombolysis might be less effective for occlusive clots than catheter-directed thrombolysis because of the difficulty in the drug penetrating thrombi.

The average total urokinase dose in one previous report of catheter-directed infusion thrombolysis of a multicentre registry was 7.8 million IU,21 and major bleeding complications were reported in 11% of patients in this study.21 More than 2000–2500 IU/kg/h (2.88–3.6 million IU/day for patients weighing 60 kg) was used in another previous report of catheter-directed infusion thrombolysis.16 The results of this study indicated that a much lower daily urokinase dose (0.72 million IU/kg/h (2.88–3.6 million IU/day) was sufficient to lyse the thrombus and recanalise the occluded vein when using pulse-spray pharmacomechanical thrombolysis. This low daily dosage of urokinase might also reduce the incidence of bleeding complications.

The necessity of filter placement has been a very controversial topic in catheter-directed thrombolysis.16 Ultra-high-dose thrombolytic therapy is known to have an approximately 6% risk of fatal PTE if iliac or iliofemoral thrombosis is present without an IVC filter.34 Mewissen et al. reported that the true prevalence of
PTE was not evaluated but symptomatic PTE occurred in six of 287 patients and one was fatal during catheter-directed thrombolysis. One study demonstrated PTE in 59% of patients undergoing haemodialysis graft thrombolysis using a modified pulse-spray technique with a large pulse volume (3–5 ml). Kinney et al. reported that 54.5 and 71.4% of patients experienced new perfusion defects after pulse-spray pharmacomechanical thrombolysis with urokinase and heparinised saline, respectively, among patients with clotted haemodialysis grafts. Concerns have been raised about the risk and significance of PTE produced by this method. The prophylactic use of a non-permanent IVC filter may be appropriate to prevent clinically significant PTE during pulse-spray pharmacomechanical thrombolysis in patients with acute proximal DVT.

This study had some limitations: First, the post-treatment objective test for PTE associated with this therapy was not performed. Although symptomatic or fatal PTE did not occur in this study, the rate of asymptomatic PTE was not clarified. The safety of this method for patients with severely compromised cardiopulmonary reserve was unclear; second, further study is needed to determine the optimal dosing regimens and frequency of administration for this method; third, although clinical trials demonstrating that rapid lysis of DVT improves the long-term clinical outcome are few and limited, early thrombolysis appeared beneficial to prevent chronic venous insufficiency. Further study is necessary to evaluate the role of restoring the early patency of treated veins in the prevention of late or chronic sequelae of DVT.

Conclusions

The combination of pulse-spray pharmacomechanical thrombolysis and the prophylactic use of a non-permanent IVC filter was a safe and effective approach for treating acute proximal DVT. Future large prospective studies will be necessary to confirm the superiority of this approach in terms of early lytic rate, safety and long-term sequelae.

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References

Pharmacomechanical Thrombolysis for DVT


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