The management of deep venous thrombosis (DVT) remains a challenge because standard treatment with anticoagulation does not resolve the thrombus formed in the vein. In addition, between 20% and 80% of patients develop post-thrombotic syndrome despite adequate anticoagulation therapy (1). This debilitating condition has major medical, social, and economic consequences and has resulted in multiple strategies for thrombus removal during the acute phase of the disease. Since its first introduction in 1994, endovascular treatment of DVT with catheter-directed thrombolysis (CDT) in combination with percutaneous thrombectomy with or without stent placement has become increasingly important due to its effectiveness in eliminating DVT symptoms and in preventing secondary venous insufficiency (2).

Percutaneous mechanical thrombectomy (PMT) methods are generally used to treat lower extremity DVT in combination with CDT to increase efficiency and decrease procedure time (3). Manual aspiration thrombectomy (MAT) is seldom used to remove a thrombus for lower extremity DVT (4). This study reports on the technical feasibility, initial success, and long-term outcomes of endovascular treatment of DVT using MAT as the first thrombus removal method in patients with acute and subacute iliofemoral DVT.

**Materials and methods**

**Patients**

Between October 2003 and December 2010, 139 consecutive patients with acute (1 to 14 days) or subacute (15 to 28 days) iliofemoral DVT were treated by endovascular methods at a single tertiary care hospital. The diagnosis of DVT was established using color Doppler ultrasonography (CDUS) and confirmed by venography performed during endovascular treatment in all patients. MAT was the primary thrombus removal technique used in all patients. CDT was used only as an adjunctive method to MAT. PMT devices were not used. Patients who had a history of chronic DVT in the contralateral leg, without involvement of the common outflow tract or the inferior vena cava (IVC), were included in the study. The exclusion criteria were femoropopliteal DVT only, ages under 18 years, contraindication to administration of iodinated contrast media, pregnancy, malignancy with a short duration of estimated survival, and the presence of concurrent acute and chronic DVT in the treated extremity. Debilitated patients and patients who were over the age of 80 years were also excluded. There was no exclusion criteria set for phlegmasia cerulea dolens. All patients received endovascular intervention either on the same day or on the day following their presentation to our clinic. The criteria definitions were based on the guidelines defined by the Society of Interventional Radiology regarding lower extremity DVT (5).
on patient demography, past medical history, and venograms were available for all patients and were evaluated retrospectively. Because thrombophilia was not evaluated as a risk factor in every patient, the documented risk factors did not include thrombophilia. Venography findings were reviewed from the digital archives. Clinical follow-up, real-time CDUS examinations, and interpretation of venography findings were carried out by two interventional radiologists.

All procedures performed on humans were carried out in accordance with the ethical standards of the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all patients. All patients were given detailed information regarding endovascular treatment, which is done routinely and is the treatment of choice for both acute and subacute iliofemoral DVT in our hospital.

Procedures

All procedures were carried out in an angiography suit using digital subtraction angiography (Multistar, Siemens, Erlangen, Germany or Innova IQ-3100, GE Healthcare, Waukesha, Wisconsin, USA). The punctures were made under ultrasound guidance using 9 MHz or 13 MHz transducers (Antares, Siemens, Erlangen, Germany) using 21 G or 18 G needles. The 18 G needle was the first choice for the first puncture of a thrombosed popliteal vein to advance an angled hydrophilic guide wire (Terumo, Tokyo, Japan). Initial access to the vein was usually achieved using a high crural or low popliteal vein puncture in all patients. Access to the posterior tibial vein or the great saphenous vein was also attempted, if deemed necessary. Ascending digital subtraction venography was obtained using contrast material at each puncture site. A 5 F vascular sheath was inserted to obtain a diagnostic venogram, after which a 9 F or 10 F vascular sheath (Europa, Cordis, Roden, the Netherlands) was placed in the popliteal vein for aspiration with a 8 F or 9 F guiding catheter (Vista Brite, Cordis) connected to a 20 mL syringe. A straight-tip guiding catheter was used to aspirate from veins with a straight course (e.g., femoral vein) while an angled multipurpose guiding catheter was used for veins with a curved course (e.g., iliac vein). The guiding catheter was advanced without a guide wire. Aspirations were performed from the caudal to cranial ends. The thrombus was gently aspirated during the advancement of the catheter. When removing the catheter, negative pressure was applied. The most cranial part was aspirated last to prevent embolization of a thrombus fragment. If there was tortuosity of the vein or resistance to the advancement of the catheter, the guiding catheter was advanced over a guide wire or the tip of the angled guiding catheter was rotated for safe advancement to prevent dissection. If there was a subacute thrombus adherent to the wall that was resistant to aspiration with a straight catheter in a straight vein, an angled guiding catheter was used. The angled guiding catheter was directed toward the venous wall to successfully aspirate the thrombus. If there were large burdens of thrombi in the IVC, a retrievable IVC filter was used, which was removed as soon as possible. CDT was used to dissolve the thrombus in the crural veins in selected patients or to dissolve the residual thrombus in the femoral and iliac veins. Tissue plasminogen activator (Actilyse, Boehringer Ingelheim, Rhein, Germany) at a dose of 1 mg/h was used as the thrombolytic drug and was delivered through a multi-side hole infusion catheter (Cragg-McNamara Valved infusion catheter, ev3, Irvine, California, USA). Venography was repeated every 8–12 hours during CDT. After removal of thrombi from the femoropopliteal veins, additional pelvic venograms were obtained during the procedure for detailed evaluations of the iliac veins and the IVC. If there was significant compression of the left common iliac vein with intraluminal webs consistent with iliac vein compression (May-Thurner) syndrome, or if there were irregularities or residual thrombi that could not be removed with MAT or CDT in the iliac veins or the IVC, self-expanding stents were placed and dilated with a balloon catheter. Stents were not placed in the femoral or popliteal veins; in rare cases, however, an iliac vein stent was extended to the common femoral vein to increase the flow into the proximal veins.

Therapeutic-level heparin was administered during the procedure, with a target partial thromboplastin time of 60 to 90 s. If the procedure was an outpatient procedure and if the treatment was successfully completed in one session, the patient was sent home on the same day on low molecular weight heparin and oral warfarin sodium. Low molecular weight heparin was stopped when the international normalized ratio reached therapeutic levels between 2 and 3. Warfarin sodium was maintained for at least six months. A follow-up visit was performed at 1, 3, 6, and 12 months and then annually; the visits included a clinical examination and CDUS. Venography was recommended for all patients at one or three years of follow-up and/or when there was any doubt about the patency of the iliac vein.

Definition of criteria

Removal of the thrombus was scaled as minimal (grade I) if <50% was removed; partial (grade II) if between 50% and 95% was removed; and complete (grade III) if >95% of the thrombus was removed. Technical success was defined as more than 50% clot removal with uninterrupted venous flow. The criteria for valvular reflux was greater than one second valve closure time with a Valsalva maneuver or after distal compression and release using CDUS in the standing position. The severity of postthrombotic syndrome was classified according to the CEAP classification. The patency of the veins was determined using venography or CDUS.

Statistical analysis

Data were expressed as the mean±standard deviation for the continuous variables and percentages for the categorical variables. A two-tailed student t test was used to compare the continuous variables. A Chi-square test was used to compare the categorical variables. Logistic regression was used to evaluate the independent risk factors. Stent patency was estimated by using the Kaplan-Meier method and comparisons of patency were made with the log rank test. A P value < 0.05 was considered to be statistically significant. Statistical analysis was performed using a computer software (Statistical Package for Social Sciences version 13.0, SPSS Inc., Chicago, Illinois, USA).
Figure 1. a–d. A 57-year-old woman with right-sided acute iliofemoral deep venous thrombosis. The venograms obtained after the right popliteal vein puncture shows acute thrombosis up to the right common femoral vein in the prone position (a, b). The same vein is patent without residual thrombus after manual aspiration thrombectomy using a 9 F guiding catheter (c, d).

Results

Demographic information of the patients in the study is shown in Table 1. DVT was acute in 110 patients with a mean symptom duration of 5.8 days. DVT was subacute in 29 patients with a mean symptom duration of 19.5 days. All patients had swelling, 44 patients (32%) had leg pain, 19 patients (14%) had significant swelling without cyanosis (phlegmasia cerulea alba), and six patients (4%) had phlegmasia cerulea dolens. There was at least one risk factor for the development of DVT in 98 patients (71%). Twenty-one of these 98 patients (22%) had two or three risk factors (Table 2). Pulmonary embolism (PE) was present before or at the time of admission in 16 patients (12%).

The popliteal vein was the only point used for access in 126 limbs, whereas the posterior tibial vein was used in addition to the popliteal vein in 22 limbs. Venous involvement was up to the common femoral vein in seven limbs, up to the common iliac vein in 114 limbs (77%) and up to the IVC in 27 limbs. Moreover, 38 patients with iliofemoral DVT had patent crural and popliteal veins.

Thrombus removal was complete (grade III) in 98 limbs (66.2%), partial (grade II) in 45 limbs (30.4%), and minimal (grade I) in five limbs (3.4%) (Fig. 1). CDT was used in 38 patients (27.3%), always as an adjunctive treatment following MAT. The dose of the tissue plasminogen activator ranged from 10 to 41 mg (mean, 19.8±12.3 mg). The duration of treatment ranged from 1 to 4 days (median, 1 day). Seventy-three patients (53%) were discharged on the same day.

At least one stent was placed in 99 limbs (67%), with all of the stents in the external iliac vein or in the common iliac vein (Fig. 2). Stents were self-expanding Wallstents (Boston Scientific, Galway, Ireland) in 80 limbs and niti-nol stents (Protégé, ev3 Inc., Plymouth, Minnesota, USA) in 19 limbs. The stent diameters ranged from 12 to 16 mm. The number of stents placed in each limb ranged from one to four. Nine patients (6%) had a filter placed in the infrarenal IVC just before treatment. IVC filters were removed at the end of the first intervention in five patients and within 14 days in three patients.

<table>
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<th>Table 1. Demographic features of patients</th>
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<td>Age, mean (range)</td>
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<td>Male, n (%)</td>
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<tr>
<td>Female, n (%)</td>
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<td>Acute thrombosis, n (%)</td>
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<td>Subacute thrombosis, n (%)</td>
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<td>Location of thrombosis, n (%)</td>
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<th>Table 2. Risk factors for the development of iliofemoral deep venous thrombosis (DVT) in 98 patients</th>
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<td>Risk factor</td>
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<tr>
<td>Previous DVT</td>
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<td>Postoperative state and/or trauma</td>
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<td>Immobilization</td>
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<td>Malignancy</td>
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<td>Postpartum state</td>
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<td>Hormonal therapy</td>
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<td>Inferior vena cava filters</td>
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<td>History of femoral catheterization</td>
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<td>Coagulation abnormality</td>
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In one patient, the filter contained a thrombus that was seen, via venography, after one week of intervention. This thrombus did not clear with anticoagulation after three weeks, and the filter was not removed. Fifty-eight patients (42%) had May-Thurner syndrome. Left side involvement was more common among females (66%) than among males (53%), although the difference was not significant ($P = 0.10$).

Technical success was achieved in 134 patients (96%). The total procedure time ranged from 22 to 165 min (mean, 60 min) while fluoroscopy time ranged from 3 to 32 min (mean, 14 min). All six patients with phlegmasia cerulea dolens had successful endovascular treatment. Five patients survived without amputation although one patient died of multi-organ failure three days after the intervention. Re-thrombosis occurred in 27 patients (19%). Re-interventions were performed in 20 of 27 patients, with successful restoration of the venous flow in 13 patients. Femoral vein insufficiency was absent in 64 (57%) and present in 48 (43%) of the 112 patients on long-term follow-up. Sixty-eight (61%) of the 112 patients were asymptomatic on follow-up. Among the patients with symptoms, seven had a CEAP score of 2, 24 had a CEAP of 3, 10 had a CEAP of 4, and three had a CEAP of 5. The three patients with a CEAP score of 5 had unsuccessful repeated interventions and worsening symptoms.

Primary and secondary patency rates were 77%, 74%, 72%, and 93%, 78%, 78% at one, three, and five years, respectively (Fig. 3). Log rank test results showed that primary patency was significantly shorter among postpartum patients ($P < 0.01$) and in patients with IVC thrombosis ($P < 0.01$).

Re-thrombosis was more frequent among postpartum patients ($P < 0.001$), patients who had IVC involvement ($P < 0.01$), and those who had extension of the stent to the common femoral vein ($P = 0.02$), according to univariate analysis. None of these factors was an independent risk factor, according to multivariate analysis. May-Thurner syndrome was more frequently seen in postpartum patients ($P < 0.05$) and in patients who had patent crural and popliteal veins before treatment ($P < 0.05$). Univariate analysis showed that patients were more likely to be asymptomatic upon long-term follow-up when DVT was acute as opposed to subacute ($P < 0.05$), when the popliteal vein was patent before the endovascular procedure ($P < 0.01$), when the thrombus removal was complete (grade III) ($P < 0.05$), when there was no re-thrombosis ($P < 0.01$), and when
there was no femoral vein ($P < 0.01$) or saphenous vein insufficiency ($P < 0.01$). However, none of these results reached statistical significance in the multivariate analysis. Multivariate analysis also showed that symptom duration ($P = 0.01$ [95% confidence interval, 1.03–1.22]) and re-thrombosis ($P = 0.01$ [CI, 0.07–0.75]) were independent variables predictive of femoral vein insufficiency in the long term.

Sixteen patients (12%) had 14 minor and two major complications. Five patients (4%) had a small hematoma at the access site (three patients had CDT) whereas four patients had short local dissection of the vein wall during aspiration thrombectomy that did not limit flow nor require treatment. Two patients had a PE that caused less than 10 min of circumoral cyanosis, cough, and a drop of approximately 10% in oxygen saturation. The symptoms spontaneously resolved within minutes. One patient had a localized but flow-limiting dissection in the iliac vein and required stent placement. Another patient had a prominent PE with significant shortness of breath. This patient had been admitted to the intensive care unit two days earlier because of an acute massive PE due to acute iliac vein thrombosis.

Two patients with unilateral DVT developed contralateral DVT within three months of the procedure. Venography revealed that the thrombosis was due to caval extension of the previously placed iliac vein stent. Both of these patients had repeated interventions with stent placement in the contralateral leg with successful outcomes. This observation is important because endovascular treatment of DVT with iliac vein stenting (e.g., malpositioning or improper positioning of the iliac vein stent) became a risk factor for the development of DVT on the contralateral side.

Discussion

This study showed that aspiration thrombectomy is an effective method to remove clots among patients with acute as well as subacute phases of iliofemoral DVT. Sixty-six percent of patients had complete thrombus removal. Re-thrombosis was not infrequent and mostly occurred during the first postprocedural month. The absence of symptoms and femoral vein insufficiency was quite high despite the extensive nature of the disease. CDT through the popliteal vein removes the thrombus in the femoral and iliac veins but also has a therapeutic systemic effect on thrombi in the crural veins. Only one-fourth of the patients who had adjunctive CDT after MAT were associated with this therapeutic effect. It may be more effective to treat patients, especially younger patients with active lifestyles, with aspiration thrombectomy through the popliteal vein and via CDT through the posterior tibial vein. On the other hand, a major bleeding complication is not present with MAT alone and could be a good strategy for certain patients.

DVT presents with differing severities of clinical manifestations. Crural vein thrombosis is the mildest, whereas iliofemoral DVT is usually the worst clinical complication. The main goals of all treatment modalities for DVT are to resolve patient symptoms by removing the thrombus as well as to prevent PE and post-thrombotic syndromes. The standard of care for the treatment of acute DVT involves anticoagulation. It has no direct thrombolytic effect, does not promote lysis to reduce the thrombus load, and does not contribute to the restoration of venous valvular function. As such, anticoagulation alone does not protect the limb from post-thrombotic syndrome, which can occur months or years after the acute thrombotic episode. If the body effectively lyases the clot early in the course of the disease, venous patency is restored and valve function can be preserved (6). However, the degree of spontaneous lysis is variable and generally unpredictable. Although approximately 90% of femoropopliteal veins occluded by a thrombus will recanalize within one year, if the iliofemoral vein is involved then only <5% will recanalize (7). Furthermore, up to 90% of patients with symptomatic, iliofemoral DVT develop significant symptoms of the post-thrombotic syndrome despite receiving anticoagulation therapy (8,9). Patients with iliofemoral DVT treated with anticoagulation alone have a poor quality of life, with 5% to 15% developing venous ulcers within five years (7,10,11). These observations have led clinicians to adopt a treatment strategy involving early thrombus removal, especially for patients with iliofemoral DVT, to improve long-term quality of life.
Thrombolysis is an attractive therapy because it involves early thrombus removal, and therefore, provides early restoration of venous patency and preservation of venous valves. The multicenter Venous Registry, the largest published study to date, reported complete lysis of lower extremity thrombi in 31%, partial lysis (50% to 99%) in 52%, and poor (<50%) lysis in 17% of the 287 patients who were treated with CDT (12). The registry included patients with chronic DVT (16%), acute episodes with concurrent chronic DVT (19%), and acute DVT (66%). Adjunctive stenting was performed in approximately 40% of patients with iliofemoral DVT. Overall, thrombosis-free survival was observed in 60% of patients after one year. Patency was much higher in patients who had complete lysis after initial treatment than those who had partial or poor lysis. Sixty-two percent of patients with <50% lysis had venous valvular incompetence, whereas 72% of patients with complete lysis had normal valve function. Six patients suffered from PE during treatment. Three studies have evaluated venous valve function after thrombolysis. Elsharawy and Elzayat (13) found that significantly fewer patients (only two of 18) developed reflux six months after treatment with thrombolysis as compared to seven (41%) in the group treated with anticoagulation. Ly et al. (14) reported that nine out of 28 patients (33%) developed reflux at two years of follow-up, which was apparently negatively related to the degree of lysis (i.e., less reflux led to a better degree of lysis). Søløsen et al. (15) reported that only two out of 42 (4%) patients who were treated and who had patent veins developed reflux. There has been only one randomized trial involving 35 patients that reported the difference between CDT and anticoagulation. Thus, additional randomized controlled trials are needed to determine both short-term and long-term results of catheter-based endovascular treatments compared to anticoagulation (13).

The main disadvantage of CDT is thought to be the increased risk of bleeding complications. In a pooled analysis, the cumulative major bleeding rate was 8%, which included any bleeding that was severe enough to result in death, surgery, cessation of therapy, or blood transfusion. Most bleeding events were confined to the vascular access sites (16). An analysis of studies after 1989 shows a decrease in the major bleeding rate to 4.8%, which presumably demonstrates an improvement in patient selection and in endovascular techniques (17). Other issues that have limited the acceptance and use of CDT include the cost of the thrombolytic agent, long infusion times, and need for long hospitalization and intensive care monitoring. In the current study, MAT was sufficient to remove almost all thrombi and eliminated the need for CDT in most patients. In other patients who required CDT, the dose of the thrombolytic agent was quite low because the majority of the thrombus was removed with aspiration thrombectomy. This is probably the most important advantage of MAT over CDT.

Symptomatic PE during surgical thrombectomy is an infrequent occurrence, reportedly occurring in 0% to 3% of patients (18). The incidence of symptomatic PE and fatal PE during CDT was 1% and 0% to 0.2%, respectively (12, 19). PMT alone had a higher rate of PE complications when used for hemodialysis graft declotting but not when used for DVT treatment (20). Patients at the highest risk for procedure-related PE were those with a non-obstructive or free-floating thrombus in the IVC. The rate of PE seen in this study with the use of MAT was similar to the rate of PE with CDT reported in the past literature.

PMT methods have emerged to increase the speed of thrombus removal and to decrease the dose of the thrombolytic agent, thereby decreasing bleeding complications. These devices can be used either with or without a thrombolytic agent and involve mechanical maceration or disruption of the clot to facilitate fast and complete clot removal (21). The rate of thrombus removal is similar between PMT and CDT, although PMT is associated with a shorter treatment time, shorter intensive care unit and hospital stays as well as reduced hospital costs. The patient may be successfully treated in a single session (22). The main disadvantages of PMT in the treatment of DVT are device costs, incomplete thrombus removal, embolization risk, learning curve associated with each device and potential to harm the venous wall or the venous valve. MAT has been used to remove thrombi in lower extremity arteries (23, 24). It is inexpensive, rapid, and simple to perform and learn; it is a key technique for mechanical thrombectomy. However, it is not frequently used in clinical practice. MAT has been used to treat lower extremity DVT in combination with thrombolysis (25). The effectiveness of MAT as the primary method of thrombus removal has been previously reported in 27 patients with acute limb DVT. Successful recanalization without the use of a thrombolytic agent was achieved in 24 (89%) patients (26). MAT has been recommended as the first line of treatment when DVT progression is rapid and when the administration of heparin or thrombolytic agents is contraindicated (27). A previous study already reported on the outcomes of six patients in the current study with phlegmasia cerulea dolens (27). MAT has certain disadvantages, such as its requirement of large vascular sheaths and guiding catheters (8 F to 9 F). Smaller guiding catheters can be used, although they are not as effective as larger ones. Aspiration of large amounts of thrombi or aspiration of blood together with a thrombus may cause a decrease in hemoglobin levels. Such blood loss may be a significant factor in patients who have a history of anemia.

This study has several limitations. First, there is a potential for recall bias because of the retrospective nature of the study. Aspiration thrombectomy removes considerable amounts of blood in addition to the clot, and a drop in the hemoglobin level should be expected after the procedure. However, we did not check the hemoglobin levels for each patient. A clinical severity score was not used over the long term. Although it is not a common practice to use such a score after endovascular treatment of DVT, it should be a part of future studies that assess patients over long-term follow-up.

As a conclusion, MAT is an effective endovascular treatment method for acute as well as subacute iliofemoral DVT. It has the major advantage of rapid thrombus removal with no bleeding complications, making outpatient treatment possible. Re-thrombosis is not rare, especially in postpartum patients, and mostly occurs in the first postprocedural month.
Conflict of interest disclosure
The authors declared no conflicts of interest.

References