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Daily Catheter-directed Single Dosing of t-PA in Treatment of Acute Deep Venous Thrombosis of the Lower Extremity

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Abstract

The strong fibrin affinity of recombinant tissue plasminogen activator (rt-PA) theoretically obviates continuous infusion or replacement of t-PA after direct intrathrombic injection. This hypothesis led the authors to evaluate single daily catheter-directed injection of rt-PA as a thrombolytic treatment for acute deep vein thrombosis of the lower extremity. Once-daily injection of rt-PA was performed in large thrombosed veins (popliteal or larger) with use of pulse-spray catheters and in small thrombosed veins in patients' calves with use of 3–4-F coaxial catheters. Patients received only full systemic anticoagulation on his/her patient care unit. This dosing regimen has been tested in 10 patients (12 legs) with a maximum dose of 50 mg per leg per day. Extensive thrombolysis was achieved in nine patients and partial thrombolysis was achieved in one patient, at an average total dose of 106 mg of rt-PA per leg. Minor bleeding was seen in three patients and no transfusions were needed. Our technique and the rationale for this pilot study is the focus of this article.

Keywords

Thrombolysis; Thrombosis, venous; Tissue-type plasminogen activator

ANTICOAGULATION, although highly effective in the prevention of pulmonary embolus, is known to be an inadequate treatment for restoration and preservation of venous function in patients with acute deep vein thrombosis (DVT) of the lower extremity (1–7). In an effort to develop a safe and more affordable thrombolytic regimen for DVT, and borrowing from favorable experience with treatment of upper extremity thrombosis associated with central venous catheters (8), we have begun to evaluate single daily intrathrombic injection of recombinant tissue plasminogen activator (rt-PA) as the basis of a thrombolytic regimen for DVT. This approach is based on the strong fibrin affinity property of rt-PA and prolonged fibrinolytic activity of fibrin-bound rt-PA, which should permit single daily dose administration and eliminate the need for continuous infusion or replacement of this thrombolytic enzyme. As preliminary results of our study have recently been reported (9), this article will focus on the techniques and rationale used in the design of this treatment regimen. Basic features of this regimen are: (i) limitation of maximum single daily rt-PA dose to 50 mg per leg and a limit of four rt-PA treatments per leg, (ii) intrathrombic hand injection of rt-PA with use of pulse-spray catheters in large veins (popliteal and larger) and gentle injection of rt-PA into thrombosed veins in the calves with use of 3–4-F coaxial catheters, and (iii) standard

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full-dose systemic anticoagulation with heparin during thrombolytic therapy, followed by oral anticoagulation therapy for 6 months.

MATERIALS AND METHODS

Patient Profiles

Ten patients (12 legs) with DVT ranging from inferior vena cava thrombosis to bilateral calf vein thrombosis (Fig 1) to unilateral popliteal and calf vein thrombosis underwent this regimen. Additional details are found in a recent publication (9).

Catheterization Approaches

Intralot injections of rt-PA were made with 4-F pulse-spray catheters (2 cm infusion length; Angiodynamics, Queensbury, NY) into large veins (popliteal and larger veins) by brisk hand injections of 0.5–1.0-mL aliquots of rt-PA spaced approximately 30 seconds apart. Smaller calf vein thrombosis was treated with more controlled hand injection of rt-PA through 3–4-F hydrophilic coaxial catheters (Cook, Bloomington, IN; Boston Scientific/ Medi-tech, Watertown, MA) negotiated past the numerous valves with small 0.018-inch hydrophilic guide wires (Meditech “gold” Glidewires; Boston Scientific/Medi-tech) in a retrograde direction (Fig 2). A single venipuncture was used for catheterization when thrombus failed to extend to the popliteal or femoral catheterization sites in the involved extremity via antegrade popliteal catheterization or retrograde femoral catheterization, respectively. In most cases, however, thrombus extended from calf veins to iliac veins or higher, necessitating introduction of antegrade and retrograde catheters in “criss-cross” fashion from either the femoral or popliteal entry sites. Because blood return is not obtained even with successful venipunctures of thrombosed veins, venipuncture is performed under direct visualization with real-time US (Hitachi Model EUB-405U; Hitachi, Tokyo, Japan) equipped with a custom needle guide. In one case in which US visualization of the popliteal vein was suboptimal, successful venipuncture was achieved with use of portable CT (Phillips Tomoscan M guidance).

During retrograde catheterization of thrombosed calf veins, both muscular (gastrocnemius) and deep veins of the calf are injected with rt-PA, but our priority is to treat posterior tibial and peroneal divisions. Each division of the three named calf veins is often duplicated, but, fortunately, small communicating veins near the ankle allow rt-PA injected down one vein to treat the companion vein as well (Fig 2b).

After intraclot rt-PA injections, the catheters are exchanged for 4-F dilators to maintain access, infuse heparin, and perform contrast venography the following day to assess patency and need for additional rt-PA. In this series, we did not use introducer vascular sheaths primarily because the intravascular portions of the sheath would result in untreated areas in which they overlap. Avoidance of sheaths allowed us to restrict venotomy size to the 4-F size of our treatment catheters.

rt-PA Dosage

The daily dose of recombinant tissue plasminogen activator (rt-PA) is determined by the extent of DVT. We use a full vial or 50 mg rt-PA (Activase; Genentech, South San Francisco, CA) when thrombosis is extensive (involving calf veins up to the common femoral vein or higher), and reduce the dosage for lesser degrees of thrombosis. When calf vein thrombosis is present, we generally split the rt-PA dose and use approximately 40% of the dose for popliteal and calf veins and 60% of the dose for the larger venous segments. No additional rt-PA is administered when brisk antegrade flow in the deep veins has been restored; we do not attempt to dissolve all detectable thrombus. We rely on anticoagulation to clear residual thrombus after flow has been reestablished. We limit rt-PA treatments to a maximum of four daily doses.

Our rt-PA doses are based on earlier experience with treatment of central catheter-related thrombosis of the upper extremity. Recent experimental data suggest that our doses may be as much as two orders of magnitude higher than necessary (10), but these implications have not yet been verified in the clinical setting.

Anticoagulation and Hematologic Monitoring

After successful catheterization for thrombolytic therapy, systemic anticoagulation is initiated with intravenous heparinization (activated partial thromboplastin time, 50–70 sec) with use of a standard weight-based regimen (80-U/kg bolus and 18-U/kg/h initial maintenance infusion). On the second day, we begin conversion to oral warfarin (with a desired international normalized ratio of 2–3), which is continued for 6 months.

Laboratory monitoring consists of daily creatinine and complete blood counts with platelet counts, and prothrombin time, activated partial thromboplastin time, and plasma fibrinogen determinations every 6 hours. To eliminate additional venipunctures, we often place a 4–5-F peripherally inserted central catheter or jugular line, maintained on a slow saline drip to accommodate the frequent blood draws. If the fibrinogen level drops below 150 mg/dL, further rt-PA infusion is postponed to allow the fibrinogen level to recover, at which point rt-PA dosage is resumed at half the previous dose if repeat venography continues to show significant obstruction.

Adjunctive Procedures

Balloon angioplasty, venous stent placement, and mechanical thrombectomy were not used in any of these cases to assess the result of thrombolysis and anticoagulation regimen alone. These measures are considered if anticoagulation fails to maintain patency.

Ventilation-Perfusion Lung Scans

To evaluate the risk of pulmonary embolus associated with this protocol, seven patients underwent a pretreatment ventilation-perfusion (V/Q) lung scan and a repeat V/Q scan the working day after the last thrombolytic treatment.

Follow-up Examinations

Patients were followed with clinical examination, venography, and color-flow Doppler US examination.

RESULTS

Venograms obtained the day after the last dose of rt-PA indicated that nine of the 10 patients had either extensive (75%–95%) or complete (>95%) thrombolysis and that the remaining patient had partial (50%–75%) thrombolysis. Flow was reestablished in the treated deep veins in all cases. The three patients bedridden from pain associated with DVT were all relieved of pain and able to ambulate after thrombolytic therapy. At 6 months, one of these patients developed reocclusion of the popliteal vein with symptoms of mild dependent ankle edema after ambulation. Seven patients treated have remained free of symptoms in a follow-up period of 6–22 months. Additional details about the patients in this study are available in a recent publication (9).

Hypofibrinogenemia occurred in one patient after the first dose of rt-PA (50 mg) with fibrinogen level falling from 290 mg/dL to 77 mg/dL. The second dose of rt-PA was delayed 1 day to allow the fibrinogen level to increase above 150 mg/dL, at which point the patient received half the previous dose (25 mg). This patient had no evidence of bleeding complications.

Bleeding complications were minor. No patient had a decrease in hematocrit of greater than 2% or decrease in hemoglobin of more than 1 g, and no patient required blood transfusion. Some minor oozing occurred at catheterization sites and was managed by simple pressure dressings. Small calf hematomas (5–15 mL) were detected with US during treatment of our second patient. We believe this was related to our initial use of pulse-spray catheters to inject rt-PA into small thrombosed calf veins. During pulse-spray injection, we noted that some of the previously injected contrast medium used to define venous anatomy had been forced out of the venous system, producing a stain of muscle fibers (Fig 2a). It appears that small calf veins filled with thrombus do not have the capacity to dissipate the sudden pressure and volume pulse of pulse-spray injection. As a result, we changed to 4-F angled glide catheters and 3-F coaxial microcatheters for more controlled injection of contrast medium and rt-PA into the calf veins to minimize risk of vein disruption and extravasation (Fig 2b). This choice of catheter also simplifies the procedure and improves our ability to catheterize the multiple calf vein divisions with their many valves. Two patients developed remote sites of bleeding. One patient developed a left arm biceps hematoma, which appeared to be a result of the frequent automatic blood pressure measurements used to monitor the patient during rt-PA treatments. This patient had also been taking aspirin until a few days before treatment. The other patient had a history of colon cancer and developed evidence of gastrointestinal bleeding almost a week after thrombolytic therapy. A mucosal lesion was found on colonoscopy. Temporally, this case of hemorrhage appeared to be related to the anticoagulation regimen rather than to thrombolytic treatments.

Although none of our patients exhibited clinical symptoms of pulmonary embolism, pretreatment V/Q lung scans indicated that three of seven patients had evidence of pulmonary embolus before treatment. In each patient, the perfusion defects had resolved on the repeat (after thrombolytic therapy) V/Q scan after treatment for the DVT in the leg. Two other patients developed a new defect on the V/Q scan performed after thrombolytic treatment, suggesting that small pulmonary emboli can occur during therapy. The remaining two patients had normal lung scans before and after thrombolytic therapy.

DISCUSSION

Many catheter-directed thrombolytic protocols are designed for thrombolytic agents that lack fibrin affinity such as urokinase and streptokinase. With systemic administration, significant thrombolysis is achieved with the use of very large doses of enzyme to generate large amounts of circulating plasmin (with consequent depletion of antiplasmin), thereby creating a “lytic” state. Catheter-directed infusion of these agents is much more efficient because it exposes the targeted thrombus directly to high (undiluted) concentrations of thrombolytic enzyme and converts clot-bound plasminogen to plasmin at the very site where it is most needed and where it is relatively protected from neutralization by antiplasmin. But because of their lack of fibrin binding or affinity, these agents will diffuse out of the targeted thrombus and must be replaced by continuous infusion to maintain a high concentration of thrombolytic enzyme in the thrombus. Catheter-directed thrombolysis of DVT with urokinase was safe and highly effective but required large doses of enzyme and resulted in prohibitive costs (11–13). However, rt-PA binds to clot, so continuous replacement or infusion should not be necessary. Theoretically, rt-PA that escapes from the thrombus converts free or circulating plasminogen to plasmin to a lesser extent than other agents because of its fibrin specificity. However, circulating rt-PA does not distinguish between desirable or physiologic fibrin plugs or clot and targeted pathologic clot. Fibrin specificity leads to markedly enhanced fibrinolytic activity whenever rt-PA is bound to either physiologic or pathologic clot. The therapeutic index for thrombolysis with rt-PA is enhanced only by maximizing exposure of the targeted thrombus while minimizing the exposure of physiologic clot to rt-PA. We try to achieve the former by permeating or exposing the entire thrombus volume to rt-PA at high or undiluted concentration with use of mechanical

dispersion of the enzyme through pulse-spray catheters, rather than relying on low-pressure infusion and diffusion that is theoretically limited by the immediate binding of rt-PA to fibrin clot. By keeping the “lacing” of the thrombus to a short time (30 minutes to approximately 1 hour), and by eliminating the theoretically unnecessary continuous infusion, we try to achieve the second goal by minimizing the amount and duration of circulating or free rt-PA that might adsorb into desired or physiologic clot. The short half-life of circulating rt-PA ($T_{1/2}$ approximately 5 minutes) theoretically plays an important role in achieving this goal.

Full systemic anticoagulation remains an essential element of our treatment because it remains the treatment of choice for prevention and treatment of pulmonary embolism associated with DVT. This potentially life-threatening complication of DVT and the possibility of small emboli that may occur during thrombolytic therapy argue against reducing the level of anticoagulation and compromising the level of protection against embolic events. Second, our experience with treatment of central catheter-related thrombosis suggests that the maximum fibrinolytic activity of this regimen is in the first 3–6 hours after pulse-spray administration and, because the next dose will be almost 24 hours later, we rely on anticoagulation to preserve any gains achieved by thrombolysis and to allow natural fibrinolysis to clear residual thrombus after our final rt-PA treatment.

Our strategy to reduce the cost of DVT thrombolysis is threefold: (i) choice of a thrombolytic enzyme with fibrin binding so that it would remain in the thrombus without the need for continuous enzyme replacement, (ii) choice of pulse-spray injection for permeation of large thrombi to promote volume thrombolysis, and (iii) reliance on full systemic anticoagulation to clear residual thrombus when flow has been reestablished. The average total dose of rt-PA used in this study was just over 100 mg per leg (106 mg or approximately \$2,000 at current prices). Recent laboratory research suggest that lower concentrations and lower total doses of rt-PA may also be effective (10). The potential for additional cost saving and increased safety supports clinical trials to evaluate these lower doses.

It may seem paradoxical that, with our concern over cost and simplicity in thrombolytic therapy, we advocate treatment of calf vein thrombosis. When all deep calf veins are thrombosed, we are generally able to treat the posterior tibial and peroneal group of veins with the retrograde approach, but this more than doubles the technical challenges of the procedure. The first patient we treated required more rt-PA (a total of 200 mg) than all of our other patients because, at that time, we believed that only the larger veins (popliteal and higher) needed to be treated. The first 50 mg dose of rt-PA was delivered into popliteal, femoral, and iliac veins but, despite substantial thrombolysis, blood flow remained stagnant on repeat venography. In the next two treatments, we divided each 50-mg rt-PA dose and used part for pulse-spray treatment of the large veins and the other part for injection of a dorsal foot vein, with tourniquets applied to try to direct rt-PA into the deep veins of the calf. These attempts to restore inflow to the popliteal vein from the calf veins failed. Finally, on the 4th day of treatment, we performed retrograde catheterization of the popliteal vein and injected most of the 50-mg dose into the calf veins. The following day, venography demonstrated brisk flow in the popliteal and femoral veins, indicating that no additional rt-PA was necessary. It appears that the restoration of inflow, a principle established in treatment of arterial disorders, appears to be valid here as well (14), and our overall rt-PA dose requirements have been lower since we made the decision to treat thrombosed calf veins right from the start.

But perhaps the most important reason to treat these smaller veins is fundamental to why the 1980 National Institutes of Health Consensus Conference recommended addition of thrombolytic therapy: the goal of restoring vein function and prevention of chronic venous insufficiency (7). If prevention of pulmonary embolus were the only goal of therapy for lower extremity DVT, there would be little reason to treat the small volume of thrombus associated

with isolated calf vein thrombosis. However, physiologic studies indicate the importance of a “calf pump,” in which contraction of calf muscles during normal ambulation can generate pressures in excess of 250 mm Hg to facilitate venous return from the lower extremities as long as these veins are patent (15,16). It is logical to infer that, when outflow from these veins is compromised or when the valves are incompetent, local venous hypertension and congestion may occur, and a number of studies have implicated the importance of preservation of function in the veins of the lower leg in prevention of post-phlebotic syndrome and venous ulcers (17–20). As the goal of thrombolytic therapy is the prevention of chronic sequelae from DVT, interventionalists need to make certain that all the resources and energies expended in this effort do not fall short of this goal. Further study is needed to determine the role restoring patency of the calf veins plays in the prevention of late or chronic sequelae of DVT.

The treatment of calf vein thrombosis adds additional challenges to a procedure that is already challenging. Performing a single wall puncture of a nonpalpable thrombosed deep vein is probably best accomplished under direct US visualization. Retrograde catheterization of calf veins, which we performed, is more difficult than antegrade catheterization because the valves are designed to resist passage in this direction, and when thrombosis is present, this difficulty is compounded. In addition, anatomically, valves are more numerous in the peripheral veins of the leg than in the larger central veins. In addition, because one is injecting thrombolytic enzymes, it is important to perform this task as atraumatically as possible (Fig 2). Fortunately, the procedure-related hematomas we have seen are small, localized, and non-life-threatening. It is likely that these complications are less serious than those seen with arterial procedures because of the lower pressure of the venous system.

The catheterization access routes we have described indicate only the approaches we have used to inject rt-PA into thrombosed calf veins. They are not intended to represent the “best” approach. In fact, retrograde catheterization of calf veins from the popliteal approach is best applied only with the “classic” anatomy of a single popliteal vein collecting venous return from calf veins that join below the level of the knee joint. Unfortunately, there is much variation in this area, including duplication of popliteal or superficial femoral vein and high popliteal bifurcations (Fig 1b) and trifurcations well above the knee joint (21) that could make it impossible to catheterize multiple calf veins from a single popliteal approach. If the anatomy was known before the start of thrombolytic therapy, the approach could be planned optimally, but many patients have such extensive thrombosis that the popliteal and calf veins are not visualized on initial venography and the particular anatomy that is present is realized only with direct contrast injection after the interventionalist has already committed to a particular access route. Alternative antegrade catheterization of calf veins has been described by other investigators (12,22) and has many potential advantages, but it is unclear how often this can be accomplished and how many groups of calf veins can be treated from this approach. There is room for improvement in catheterization techniques for treatment of calf veins.

Offsetting the technical challenges posed by this method are some other advantages to the single daily rt-PA dose treatment for DVT, beyond just the reduction in cost of thrombolytic enzyme. By administering thrombolytic enzyme only in the interventional radiology suite, the intensive care hospitalization required with continuous infusions of thrombolytic enzyme is avoided and the errors and interruptions in thrombolytic enzyme infusion that occasionally occurred with continuous infusion regimens are eliminated. Second, the method obviates the additional trips back to the radiology suite needed to reposition infusion catheters to optimize delivery of urokinase to new areas of residual thrombus and minimize the amount of wasted enzyme diverting into nearby collateral veins. In principle, the direct intraclot injection of rt-PA allows the interventionalist optimal control over distribution of the thrombolytic agent, whereas with slow continuous infusions, distribution is largely controlled by local flow dynamics and presence or absence of nearby collateral veins. With direct intraclot injection of

a thrombolytic agent that binds to fibrin, distribution of the enzyme is dependent only on the skills of the interventional radiologist in catheterizing different branches. Thrombolysis occurs concurrently in all branches injected with rt-PA, so thrombolysis proceeds in parallel, whereas continuous-infusion thrombolytic regimens allow only a serial or sequential thrombolytic process unless multiple selective catheters are placed and infused simultaneously. Our experience with this regimen indicates that the technical challenges can be met by the experienced interventional radiologist, and we are hopeful that further evaluation and modification of this approach will finally lead to a safe, affordable, and more complete treatment option for acute DVT of the lower extremity.

Abbreviations

DVT, deep vein thrombosis; rt-PA, recombinant tissue plasminogen activator; V/Q, ventilation/perfusion.

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Figure 1.

Bilateral lower extremity and inferior vena cava (IVC) thrombosis after IVC filter placement treated with 100 mg rt-PA per leg. **(a)** Pretreatment (left) venogram (injection of lower IVC) shows contrast material pooling in interstices of thrombus in the IVC and both iliac veins. Thrombosis extended into femoral, popliteal (not shown), and calf veins bilaterally. Posttreatment (right) venogram shows clearance of thrombus from left iliac and femoral veins. **(b)** Left popliteal veins and calf vein thrombosis (left) cleared after treatment with rt-PA (right). Note the calf veins group into anterior (*a*) and posterior divisions (*p*), which join just above the knee joint space to form the popliteal vein. Variations in the popliteal vein are common.

There is contrast media in subcutaneous fat (*E*) from test injection during the initial catheterization venipuncture attempt, which proved to be superficial to the popliteal vein.

Figure 2.

Treatment of calf vein thrombosis (retrograde catheterization). **(a)** Rapid pulsed injection of rt-PA through pulse-spray catheter (arrowheads) into a small thrombus-filled calf vein can cause extravasation of previously injected contrast media into muscle (striated pattern; arrows). The patient developed a small (approximately 5 mL) hematoma during therapy. **(b)** Gentle hand injection of contrast media (or rt-PA) through a 3-F catheter (introduced through a coaxial 4-F catheter) allows one to treat both the catheterized calf vein (1) and its companion vein (2) via small communicating veins (arrows) with a lower risk of extravasation or vein rupture.