Usefulness of catheter-directed thrombolysis using alteplase in peripheral vascular occlusion

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This study evaluated the safety and efficacy of alteplase in catheter-directed treatment for peripheral arterial and venous thrombosis and considered the optimal dosing regimen. Forty-four patients (49 encounters) underwent transcatheter therapy using alteplase between January and November 1999. The most common indications for thrombolysis were peripheral arterial occlusion (PAO) and venous thrombosis (38 patients, 43 encounters). Each encounter was reviewed for indication, dosage of alteplase, duration of infusion, concomitant use of anticoagulation, degree of lysis, and complications. Patients were divided into low-dose (0.5 to 1.0 mg/hr), mid-dose (1.0 to 1.5 mg/hr), and high-dose (>1.5 mg/hr) groups. For PAO, there was no significant difference in the success rate between the 3 dose groups. A lower complication rate was achieved in the low-dose

group. For venous thrombosis, there was no difference in the overall success or complication rates for each of the 3 groups. Partial lysis was achieved more readily in the mid- and high-dose groups, but the risk of serious complications was greater. Overall, the complete thrombolysis rate was 71% for PAO and 55% for venous thrombosis. Major and minor complication rates were 7% and 19%, respectively. An equivalent success rate with a lower complication rate can be achieved using a low-dose constant catheter-directed infusion of alteplase for cases of PAO. Cases of venous thrombosis had a lower overall success rate compared with PAO. A mid-dose infusion of alteplase can achieve greater complete and partial thrombolysis rates without increasing the complication rate. Major and minor complication rates were similar to the rates given in the published literature.

Concerns about potential viral contamination of urokinase, obtained from fetal kidney cell tissue cultures, led the Food and Drug Administration to ban its sale and distribution in January 1999 (1). These restrictions have created an urgent need for information about alternative thrombolytic agents. Four other plasminogen activators remain available in the USA: streptokinase, anistreplase, retavase, and alteplase. Streptokinase is inexpensive and has a well-established track record. However, the use of streptokinase, as well as its stabilized intermediate, anistreplase, is limited due to its antigenic potential and lower efficacy (2). Retavase is a recombinant mutein of alteplase, but only recently have preliminary studies on its use in catheter-directed thrombolysis been reported (3).

In recent years, alteplase has been studied in a number of trials to assess its effectiveness in peripheral vascular thrombolysis. Although approved by the Food and Drug Administration only for management of acute myocardial infarction, acute massive pulmonary embolism, and acute ischemic stroke, alteplase has increasingly become the thrombolytic agent of choice for the treatment of peripheral arterial and venous thromboses.

At the present time, many radiologists and other clinicians in the USA lack experience with alteplase. This retrospective study of our experience at Baylor University Medical Center using alteplase in catheter-directed thrombolysis for peripheral vascular occlusion was performed to evaluate its efficacy and safety and to establish an optimal dosing regimen.

MATERIALS AND METHODS

Between January and November 1999, 44 patients (49 encounters) underwent transcatheter therapy with alteplase at Baylor University Medical Center in Dallas. The vast majority

of the cases (38 patients, 43 encounters) involved either peripheral arterial occlusion (PAO) or deep venous thrombosis (DVT). Other indications included thrombosis of the intracranial carotid artery, superior mesenteric artery, hepatic vein, and dialysis graft. One patient underwent >24 hours of therapy for a presumed thrombus within the inferior vena cava, which later was discov-

Table 1. Summary of alteplase thrombolysis cases at Baylor University Medical Center from January to November 1999

Indication	Patients (No.)	Encounters (No.)
Peripheral arterial occlusion	18	21
Superior vena cava syndrome	9	9
Effort vein thrombosis	6	6
Iliofemoral deep vein thrombosis	5	7
Intracranial arterial occlusion	2	2
Mesenteric arterial occlusion	1	1
Budd-Chiari syndrome	1	1
Arterial-venous dialysis graft occlusion	1	1
Inferior vena cava "thrombus"	1	1
Total	44	49

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Table 2. Results of alteplase treatment in 21 cases of peripheral arterial occlusion

Alteplase dosage (mg/hr)	Lysis			Complications	
	Complete	Partial	None	Major	Minor
<1 (n = 6)	4	1	1	0	0
1 to 1.5 (n = 7)	6	1	0	0	3
>1.5 (n = 8)	5	2	1	1	2
Total (n = 21)	15 (71%)	4 (19%)	2 (10%)	1 (5%)	5 (24%)

Table 3. Results of alteplase treatment in 22 cases of deep venous thrombosis

Alteplase dosage (mg/hr)	Lysis			Complications	
	Complete	Partial	None	Major	Minor
<1 (n = 5)	3	1	1	0	1
1 to 1.5 (n = 9)	5	4	0	0	2
>1.5 (n = 8)	4	4	0	2	0
Total (n = 22)	12 (55%)	9 (41%)	1 (5%)	2 (9%)	3 (14%)

ered to represent tumor invasion. The indications and numbers of patients and encounters are listed in *Table 1*.

Each patient chart was reviewed for age, sex, and indication. Each treatment was then evaluated for the following:

1. Degree of lysis: complete lysis (<5% residual thrombus, resolution of clinical symptoms), partial lysis (>5% residual thrombus, $\pm$ resolution of clinical symptoms), or no lysis (no change in clot burden, no clinical improvement)
2. Dosage of alteplase: total dose, infusion duration, and mean dose
3. Concomitant use of anticoagulation (heparin or warfarin)
4. Major complications: death, bleeding event requiring intervention or transfusion, stroke, or limb loss
5. Minor complications: bleeding events managed conservatively

RESULTS

Peripheral arterial occlusion

Twenty-one treatments with alteplase were performed in 18 patients (16 men, 2 women; average age, 67.7 years). The treatments were delivered into 19 venous and synthetic bypass grafts and 2 native arteries. In each encounter, the patient underwent thrombolysis with a nonbolus, continuous infusion of alteplase (50 mg of alteplase reconstituted in 50 mL of sterile water and diluted with 0.9% normal saline solution to a concentration of 0.1 to 0.2 mg/mL). Delivery was accomplished through multi-sidehole catheters and/or infusible wires, embedded into the occluded vessel or graft whenever possible. Alteplase dosages and infusion regimens were not standardized, ranging from 0.5 to 3 mg/hr, and were administered as either a tapered or constant infusion. In our early experience, patients tended to receive higher infusion doses with a slower rate of taper.

Table 4. Comparison of alteplase treatment for peripheral arterial occlusion and deep venous thrombosis

	Total dose (mg)	Duration of infusion (hours)	Average dose (mg/hr)
Peripheral arterial occlusion	35 ($\pm$ 23)	26 ($\pm$ 15)	1.38 ($\pm$ 0.48)
Deep venous thrombosis	41 ($\pm$ 29)	31 ($\pm$ 19)	1.35 ($\pm$ 0.36)

Table 5. Overall results of alteplase treatment in 43 cases of peripheral vascular occlusion

Alteplase dosage (mg/hr)	Lysis			Complications	
	Complete	Partial	None	Major	Minor
<1 (n = 11)	7	2	2	0	1
1 to 1.5 (n = 16)	11	5	0	0	5
>1.5 (n = 16)	9	6	1	3	2
Total (n = 43)	27 (63%)	13 (30%)	3 (7%)	3 (7%)	8 (19%)

Fourteen of 21 cases (67%) included a combination of catheter-directed thrombolysis with alteplase and peripheral systemic heparin. Heparin dosages ranged from 500 to 1000 units/hr. One patient received 3000 units of heparin during the initial procedure but did not receive a heparin infusion. Of the nonheparinized encounters, 6 were on warfarin treatment. Laboratory evaluation revealed these patients to have either a therapeutic or supertherapeutic prothrombin time. One patient did not receive either heparin or warfarin during therapy.

The average total dose of alteplase for each patient was 35.2 mg (SD, 22.8 mg; median, 24.5 mg), with an average duration of therapy of 25.9 hours (SD, 14.9 hours; median, 22.5 hours). The average dosage of alteplase was 1.38 mg/hr (SD, 0.48 mg/hr; median 1.44 mg/hr).

Complete lysis was achieved in 15 of 21 treatments (71%). One of these patients initially received 40 mg of alteplase >20 hours inadvertently infused into a chronically occluded native external iliac artery rather than into the occluded bypass graft. Partial lysis was achieved in 4 of 21 treatments (19%). Unsuccessful therapy occurred in 2 of 21 cases (10%). Of these cases, 1 patient required emergent surgery for limb ischemia and compartment syndrome before the termination of alteplase therapy and was not restudied. In the other patient, an occluded popliteal-distal bypass graft could not be traversed with either a guidewire or infusion catheter. This patient underwent end-hole catheter infusion, with the tip of the catheter positioned just proximal to the presumed origin of the graft.

Minor complications were encountered in 5 of 21 treatments (24%): all were localized hematomas at the groin puncture site. One patient (5%) suffered a major complication, requiring surgical evacuation of a groin hematoma at the puncture site. No cases of death, intracranial hemorrhage, or allergic reaction were seen.

The thrombolysis and complication results were separated into low-dose (<1 mg/hr), mid-dose (1 to 1.5 mg/hr), and high-dose (>1.5 mg/hr) groups. Only cases that achieved complete thrombolysis were considered successful, while cases with partial or no thrombolysis were considered failures. The results are presented in *Table 2*.

Deep venous thrombosis

Twenty-two treatments with alteplase in 20 patients (10 men, 10 women; average age, 44.9 years) were performed for peripheral venous thrombosis, including 15 upper extremity/superior vena cava and 7 iliofemoral DVTs. As with PAO, in each encounter the patient underwent thrombolysis with a nonbolus, continuous infusion of alteplase. Delivery was accomplished through multisidehole catheters and infusible wires, embedded into the occluded vessel whenever possible. Alteplase concentrations between 0.1 and 0.2 mg/mL were used. The dose and infusion regimens were not standardized, ranging from 0.5 to 3 mg/hr, and were administered as either a tapered or constant infusion.

Twenty of 22 cases (91%) included a combination of catheter-directed thrombolysis with alteplase and peripheral systemic heparin. Heparin dosages were not standardized and ranged from 500 to 1000 units/hr. In the remaining 2 cases, both patients were either therapeutic or supertherapeutic on warfarin and, therefore, did not receive heparin.

The average total dose of alteplase for each patient was 41.3 mg (SD, 28.6 mg; median, 27.25 mg), with an average duration of therapy of 30.6 hours (SD, 19.2 hours; median, 22.75 hours). The average dosage of alteplase was 1.35 mg/hr (SD, 0.36 mg/hr; median, 1.35 mg/hr).

Complete lysis was achieved in 12 of 22 treatments (55%) and partial lysis in 9 of 22 treatments (41%). One patient (5%) failed nearly 23 hours of thrombolysis of a common femoral vein thrombus, due to ineffective end-hole catheter delivery of alteplase and the presence of large transpelvic collateral veins.

Minor complications were encountered in 3 of 22 encounters (14%), including 2 incidences of self-limited hematuria and 1 incidence of persistent nosebleed. Two of 22 treatments (9%) resulted in a major complication. Both patients required blood transfusions during therapy: 1 for hematuria and the other for melena. No cases of death, intracranial hemorrhage, or anaphylaxis were seen.

The thrombolysis and complication results were separated into low-dose (<1 mg/hr), mid-dose (1 to 1.5 mg/hr), and high-dose (>1.5 mg/hr) groups. Only cases that achieved complete thrombolysis were considered successful, while cases with partial or no thrombolysis were considered failures. The data are presented in *Table 3*.

Summary of all patients

The overall dosage comparison between PAO and DVT is presented in *Table 4*. The total dosage of alteplase was lower and the infusion duration shorter for PAO, while the average infusion rate was equivalent. The complete lysis rate for both PAO and DVT was 63% (27 of 43 encounters). Partial and no lysis were achieved in 30% and 7%, respectively (*Table 5*). Major complications occurred in 7% of cases, and minor complications occurred in 19%. *Figures 1a–1c* demonstrate an example of al-

Figure 1. A 60-year-old woman with breast cancer, undergoing radiation and chemotherapy with a history of multiple central line placements, presented with acute facial and upper extremity swelling for 1 week. (a) Initial bilateral upper extremity and central venogram showing chronic occlusions of the bilateral brachiocephalic, left subclavian veins, and superior vena cava with extensive collateralization. (b, c) Bilateral upper extremity venogram after 24 hours of selective infusion of tissue plasminogen activator into both brachiocephalic, subclavian veins and the superior vena cava, showing complete interval resolution of the thrombosis with wide patency of the central veins. The patient became asymptomatic. Tissue plasminogen activator was infused at a rate of 2 mg/hr for a total of 24 hours.

most complete lysis of central DVT. The patient showed marked clinical improvement. *Figures 2a–2e* demonstrate an example of complete lysis of an acutely occluded femoral-popliteal graft with alteplase treatment.

Figure 2. A 43-year-old woman, who was a chronic smoker for the past 15 years, with chronic hypertension, extensive peripheral vascular disease, a history of right common iliac arterial stenosis requiring surgical placement of a left-to-right femoral-femoral graft and right femoral-to-popliteal graft in the past, presented with 1 day of acute resting right lower extremity pain. (a) Selective arteriogram of the right femoral-femoral graft anastomosis showing acute thrombosis of the right femoral-to-popliteal graft and chronic occlusion of the native superficial

femoral artery with minimal collateralization. (b) Serial runoff arteriogram showing thrombosis of the entire right femoral-popliteal graft with reconstitution of the above-the-knee popliteal artery by collateral flow. (c–e) Repeat selective arteriogram of the right femoral-popliteal graft after 12 hours of tissue plasminogen activator thrombolytic infusion showing interval resolution of the graft thrombosis with marked clinical improvement. Tissue plasminogen activator was infused at a rate of 1 mg/hr for approximately 12 hours.

DISCUSSION

Recently, numerous studies have been published that focus on the use of alteplase in peripheral vascular occlusion. Intra-arterial alteplase has been shown to be a more effective and safer treatment agent than streptokinase (4). It also has been associated with more rapid clot lysis than that of urokinase, with no significant difference in hemorrhagic complications (5). However, Ouriel et al reported an increased incidence of hemorrhagic complications with alteplase compared with urokinase, which may be related to differential dosing regimens or intrinsic pharmacologic differences between agents (6). Despite the many studies, no prospective randomized trial has been published evaluating dose regimens and method of delivery of alteplase or directly comparing alteplase with urokinase and streptokinase. Therefore, it is not possible to make a definitive statement regarding the appropriate dosages for treatment of peripheral vascular occlusion (7).

In catheter-directed therapy with alteplase for PAO, we found no significant difference in the success rate between the low-, mid-, and high-dose groups. No complications were encountered in the low-dose group, and only minor complications were encountered in the mid-dose group. Equivalent complication rates occurred in the high-dose group; however, the only major complication fell in this category. For DVT, we found no difference in the overall success or complication rates for each of the 3 groups. Partial lysis was achieved more readily in the mid- and high-dose groups but at a greater risk of more serious complications.

We achieved a complete thrombolysis rate of 71% for PAO. Our results are consistent with the published data, with success rates ranging from approximately 70% to 90% of cases (8, 9). The wide variability in success rates is partially due to varying definitions for initial technical or clinical success, as well as differences in dosing regimens (1). Compared with studies using a similar dose range, our results are equivalent (2, 10).

Most studies of alteplase use in the treatment of DVT have involved systemic administration. A few trials have examined catheter-directed thrombolytic therapy for DVT. Using urokinase, Mewissen et al achieved a complete lysis rate of 31% (34% of cases of acute DVT and 19% of cases of chronic DVT) (11). Verhaeghe et al were able to restore patency in 79% of thrombosed veins using alteplase (12). We achieved a complete lysis rate for DVT of 55% and a partial lysis rate of 41%. In general, in addition to a lower success rate, our cases of venous thrombosis required more total alteplase and longer infusion duration than those of PAO. This is likely due to the chronicity and higher clot burden in DVT.

Our overall major and minor complication rates for peripheral vascular occlusion were 7% and 19%, respectively. The major complications occurred in the high-dose group (>1.5 mg/hr). Again, no cases of intracranial hemorrhage or death were associated with alteplase therapy. Our complication results are similar to those reported by Berridge et al in a review of 19 trials of intra-arterial thrombolysis using alteplase, streptokinase, and urokinase, in which minor bleeding occurred in approximately 15% of patients and major bleeding occurred in 5% (13).

Our early experience with alteplase has demonstrated that it is an effective alternative to urokinase in catheter-directed thrombolysis for peripheral vascular occlusion; however, it is clear that further investigation is warranted in order to determine its optimal dose. Although the number of cases in each of our dose groups is relatively small, certain trends are evident. For PAO, an equivalent success rate with a lower complication rate may be achieved using a low-dose (0.5 to 1.0 mg/hr) constant infusion of alteplase. For DVT, complete and partial lysis rates increase in the mid-dose range (1.0 to 1.5 mg/hr), without increasing the complication rate. Partial lysis may aid in the overall success rate by allowing for further intervention to be performed (e.g., angioplasty, stent

placement). Overall, our complete lysis and complication rates were similar to those in the published literature.

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