◆ CLINICAL INVESTIGATION ◆

Potential Benefits From Heating the High-Dose rtPA Boluses Used in Catheter-Directed Thrombolysis for Acute/Subacute Lower Limb Ischemia

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Purpose: To explore the potential benefits from heating recombinant tissue plasminogen activator (rtPA) before catheter-directed thrombolysis in patients with lower-limb ischemia of <30 days' duration.
Methods: Over a 2-year period, 34 patients (26 men; mean age 63.5 years, range 39–80) with 10 iliac and 24 infrainguinal arterial occlusions (5 embolic and 29 thrombotic) were treated with two 5-mg boluses of rtPA injected into the proximal clot, followed by 2 additional 5-mg boluses of rtPA. In the first 18 patients (group A), room temperature rtPA was administered, whereas in the last 16 patients (group B), the rtPA boluses were heated to 38°C for 30 minutes before injection. Residual thrombus was treated with a continuous infusion of 2.5 mg/h of rtPA for 4 hours then at a reduced dose (1 mg/h).
Results: Successful thrombolysis was achieved in 28 (82%) arteries. Unmasked lesions were treated with balloon angioplasty/stenting in 17 cases and with surgery in 4. One fatal retroperitoneal hematoma occurred in group A. Heating the rtPA did not significantly alter the outcome of thrombolysis. However, a statistically significant reduction in the total rtPA dose was observed in group B (24.28 mg versus 27.9 mg in group A, $p=0.05$), as well as quicker lysis (2 hours, 42 minutes versus 6 hours, 12 minutes in group A, $p=0.001$). There was no statistical difference in the amputation-free survival at 30 days between the groups.
Conclusions: In patients with acute or subacute lower limb ischemia treated with catheter-directed thrombolysis, heating the rtPA results in faster lysis with a considerable reduction in the total dose of the lytic agent.

J Endovasc Ther 2003;10:739–744

Key words: lower limb ischemia, thrombosis, thrombolysis, recombinant tissue plasminogen activator, hyperthermic fibrinolysis, recanalization

The management of the acutely ischemic limb should include a judicious combination of both thrombolytic therapy and revascularization procedures.[1–3] The success rate of catheter-directed thrombolysis (CDT) for the initial revascularization of thrombosed native arteries ranges from 58% to 100%.[1,2,4–7] Recombinant tissue plasminogen activator (rtPA) is clearly superior to streptokinase[8] and, compared to urokinase, results in faster

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lysis[9,10]; however, there is a higher incidence of major hemorrhagic events with rtPA than urokinase.[11,12]

Several years ago, two in vitro studies showed that elevated temperature increases the fibrinolytic activity of tissue plasminogen activator.[13,14] Based on these experimental observations, we designed a prospective nonrandomized study to investigate whether this benefit can be achieved in clinical practice.

METHODS

Study Design and Patient Population

A nonrandomized study was designed to compare catheter-directed thrombolysis for the treatment of acute lower limb ischemia using rtPA boluses (Actilyse; Boehringer Ingelheim, Germany) that were either at room temperature or heated to 38°C for 30 minutes before injection. Approval by the local ethics committee for this trial was received, and all patients gave informed consent to participate.

Patients were eligible for the study if they presented with signs and symptoms of acute lower limb ischemia of <30 days' duration. Thrombotic occlusions in the upper extremities, visceral vessels, or peripheral bypass grafts were not eligible for this study. Occlusions were categorized as either thrombotic or embolic in nature. Arterial embolism was suggested on the basis of (1) sudden onset of clinical symptoms, (2) identification of an embolic source, (3) absence of preceding claudication, and (4) presence of normal pulses and Doppler systolic blood pressures in the unaffected limb.

Over a 2-year period, 34 patients (26 men; mean age 63.5 years, range 39–80) were enrolled. The average duration of symptoms was 9 days, 11 hours (range 10 hours to 30 days). The patients had 5 embolic and 29 thrombotic occlusions located in 10 iliac and 24 infrainguinal arteries; the mean occlusion length was 12 cm (range 5–28). The degree of acute limb ischemia was classified[15] as I (viable) in 7, IIa (marginally threatened) in 17, and IIb (immediately threatened) in 10. Each patient had only one occlusion in one limb treated, and only one course of thrombolytic therapy was given. The first 18 consecutive patients (group A) served as the control group, receiving thrombolysis with the rtPA at the customary room temperature. The last 16 consecutive patients (group B) underwent thrombolysis with rtPA boluses heated to 38°C for 30 minutes in a commercial heating device (Thermocult; Boehringer Ingelheim) that is used for warming intravascular contrast media.

Technique

Other than the temperature of the lytic agent, the infusion technique was the same in both groups. Two 5-mg boluses of rtPA (reconstituted 1:1 with distilled water) were injected slowly through a 5-F end-hole catheter into the proximal occlusion at an interval of 10 minutes to initiate lysis and facilitate subsequent manipulations. However, at this stage, no forceful efforts were made to get through the entire occlusion so as to prevent dissection or perforation of the artery. After bolus delivery, a 0.035-inch hydrophilic guidewire (Terumo, Tokyo, Japan) was advanced further into the occlusion. The end-hole catheter was exchanged for a 5-F Mewissen catheter (Boston Scientific, Natick, MA, USA) with either 10 or 20 side holes (5-cm or 10-cm infusion length, respectively). This catheter was positioned so that the infusion segment was within the thrombus while its tip was occluded by the guidewire. Two additional 5-mg boluses of rtPA were given 10 minutes apart. If a significant amount of thrombus remained, a continuous infusion of 2.5 mg/h of rtPA was started using a calibrated infusion pump; after 4 hours, the dosage was reduced to 1 mg/h. Heparin (500 U/h) was infused through the sheath at the same time to prevent pericatheter thrombus formation. No concomitant antiplatelet therapy was administered. Patients were monitored in the vascular department's high dependency unit for activated partial thromboplastin time, hemoglobin, platelets, and creatinine.

Follow-up angiograms were performed after 2, 4, 8, and 12 hours of continuous infusion and as needed in case of a rapidly expanding groin hematoma or worsening limb ischemia. After completion of thrombolysis, any underlying critical arterial stenosis was

TABLE
Comparison of Patient and Lesion Characteristics

	Unheated rtPA (n=18)	Heated rtPA (n=16)	p
Age, y*	62.0±10.7 (43–74)	65.0±10.9 (39–80)	0.42
Sex	15 men (83%)	11 men (69%)	0.55
Smoking	8 (44%)	11 (69%)	0.28
Diabetes	8 (44%)	5 (31%)	0.66
Atrial fibrillation	1 (5%)	4 (25%)	0.26
Viable vs. threatened	2 vs. 16	5 vs. 11	0.30
Duration ≤14 vs. >14 days	14 vs. 4	13 vs. 3	0.86
Embolism vs. thrombosis	1 vs. 17	4 vs. 12	0.26
Iliac vs. infrainguinal	4 vs. 14	6 vs. 10	0.55
Length ≤10 vs. >10 cm	6 vs. 12	5 vs. 11	0.81

* Mean±SD (range).

balloon dilated with or without stent implantation; if the lesion was too long for angioplasty, the patient was prepared for semielective surgery. If there was insufficient clinical improvement after thrombolysis, the patient went to urgent surgery without awaiting reversal of the effects of the thrombolytic therapy. These patients were continued on intravenous heparinization, but the rtPA infusions were terminated.

After thrombolysis and any complementary procedures, all patients were started on intravenous heparin for 48 hours and continued with ticlopidine for 6 weeks and thereafter with aspirin for life. Ankle-brachial index measurement and color-flow Doppler imaging were performed before patient discharge and at 1 month after the procedure.

Definitions and Statistical Analysis

A positive thrombolytic outcome was one resulting in complete recanalization (residual mural thrombus reducing the vessel luminal diameter by <5%) with restoration of distal blood flow (inclusive of any angioplasty or surgery) and abolition of ischemic symptoms for at least 30 days.

A chi-square test with Yates' correction or the Fisher exact test was used to search for any statistical differences between the groups with regard to the following variables: ischemic classification (viable versus threatened), symptom duration (≤14 versus >14 days), and cause (embolism versus thrombosis), as well as anatomical location (iliac versus infrainguinal) and length of the thrombotic occlusion (≤10 versus >10 cm). Similar tests were also applied for comparison of the 30-day amputation-free survival rates and to assess the impact of heating the rtPA on the thrombolytic outcome (positive versus negative) and on the incidence of complications. In addition, the nonparametric Wilcoxon rank sum test was used to assess any differences in total rtPA dose and duration of lysis between the groups. Statistical significance was indicated by $p \leq 0.05$.

RESULTS

There was no significant difference between the groups with regard to demographics; the classification, duration, and cause of ischemia; and the anatomical location and length of the thrombotic occlusion (Table).

Intrathrombus delivery of the rtPA boluses was achieved in all but 1 (3%) group A patient. A positive thrombolytic outcome was obtained in 28 (82%) patients: 14 in each group ($p=0.77$). Thus, heating of the rtPA boluses did not affect the outcome of the procedure. However, in patients treated with heated rtPA, there were statistically significant reductions in the total rtPA dose (group A: 27.9 mg [range 10–38] versus group B: 24.3 mg [range 20–31], $p=0.05$) and duration of lysis (group A: 6 hours and 12 minutes [range 0.33–13 hours] versus group B: 2 hours, 42 minutes [range 0.75–6 hours], $p=0.001$).

In 17 patients, successful thrombolysis was followed by prompt balloon angioplasty for underlying stenoses; in 7 iliac lesions, 1 or 2 stents (average number 1.4) were deployed to treat postangioplasty residual stenosis or flow-limiting dissections. Four patients with successful lysis underwent bypass graft placement, including reversed saphenous vein bypass grafting to the anterior tibial artery in 2 patients with thrombosed popliteal aneurysms. Seven patients (5 with an embolic occlusion and history of atrial fibrillation and 2 with thrombosed ectatic arteries) had no underlying anatomical lesion; these patients were placed on life-long anticoagulation.

In addition to the delivery failure, 5 patients had no benefit from thrombolysis. One patient underwent iliofemoral bypass for early reocclusion after external iliac artery recanalization and stenting. Another patient experienced a peroneal artery dissection after 10 mg of rtPA were delivered; below knee amputation was performed. Early rethrombosis and retroperitoneal hematoma led to fatal myocardial infarction in one patient. Distal embolization in one patient caused extensive thrombosis throughout the femoral artery; thrombectomy and aortofemoral bypass were performed. The fifth patient had vasculitis and developed early rethrombosis of the popliteal artery; minor forefoot amputation was necessary.

Bleeding complications included the fatal retroperitoneal hematoma in group A and 5 pericatheter groin hematomas (2 in group A and 3 in group B), which were controlled with prolonged manual compression. Distal embolization occurred in 3 patients (2 in group A and 1 in group B) and caused temporary worsening of ischemia; in 2 of these, the emboli were resolved with prolongation of thrombolysis and in the third with heparinization only. No statistically significant difference in the incidence of complications between the groups was found, nor was there any difference in the 30-day amputation-free survival rates (89% [16/18] in group A versus 94% [15/16] in group B, p=NS).

DISCUSSION

Recombinant tissue plasminogen activator offers the advantage of higher initial angiographic success and limb salvage compared with streptokinase.[16] Although the rates of major hemorrhagic events are higher with rtPA than with urokinase,[11,12] the thrombolytic process with this agent tends to be more rapid.[9,10] In the only randomized study comparing rtPA to urokinase,[17] there was a slightly greater effectiveness of rtPA in patients with femoropopliteal occlusions, although the difference was not statistically significant.

As a method of CDT, accelerated thrombolysis with high-dose bolus rtPA is preferable to low-dose continuous infusion regimens because it considerably shortens the mean duration of lytic therapy in acute occlusions of $<$30 days' duration without significant differences in clinical success and complication rates.[18] This is of utmost importance when prompt revascularization is required (class IIa and, particularly, IIb limb ischemia).[19] Additionally, accelerated thrombolysis with a saturating high dose of rtPA followed by a slower continuous infusion of the lytic agent appears to predict the outcome of thrombolysis; if lysis occurs during the bolus phase, the so-called "trial of lysis," the entire procedure is likely to succeed.[20] If there is no response to the initial boluses, continued infusions are justified only in limbs able to tolerate ischemia for $>$4 hours. Finally, accelerated thrombolysis with initial high-dose boluses is very convenient because the patient can be transferred to a nearby area to continue the infusion, so the angiography table becomes available for another procedure.

Despite its successful performance as a lytic agent, rtPA is associated with major bleeding events in up to 46% of the cases.[12] There is sufficient evidence that the soluble fibrin degradation products produced during thrombolysis promote systemic plasminogen activation with resultant fibrinogenolysis, which is primarily responsible for the distant bleeding seen with rtPA.[12,21,22] Because this rtPA-mediated fibrinogenolytic process is both delayed and prolonged,[23] it is reasonable to expect that shortening the rtPA protocols may reduce the potential risk for bleeding. In this context, exploration of ways to increase the activity of the lytic agent is justified.

Two relatively recent in vitro studies have

shown that elevated temperatures increase the fibrinolytic activity of tissue plasminogen activator. Yenari et al.[13] used thrombi prepared from arterial blood in phosphate-buffered solution to estimate an approximately linear decrease of 0.5% of rtPA-induced clot lysis per 1°C decrease in temperature. Schwarzenberg et al.[14] showed a nonlinear increase in rtPA-based fibrinolysis with rising temperature; in their study using fibrin clots in plasma incubated at temperatures as high as 45°C, they showed that time to lysis approximately halved from 30°C to 40°C and the concentration of D-Dimer tripled.

Although rtPA (Actilyse) remains chemically stable for 3 hours at 45°C, theoretically, lower temperatures seem also to be effective. As Aschoff et al.[24] showed, there is a decline in body temperature in the extremities even in healthy subjects; the estimated temperatures of the femoral and calf muscles and the foot are 35°C, 33°C, and 27°C, respectively. Based on these observations and to avoid the harmful effects of external heat application,[14] we heated the rtPA solution to 38°C before use, a temperature that is higher than that usually found in the lower extremities. As a result, there was a significant reduction in both the duration of lysis and the total delivered volume of rtPA in patients treated with heated rtPA. However, there were no statistically significant differences with respect to clinical outcome (30-day amputation-free survival rate) or complications between the groups. The clinical importance of these findings requires further investigation.

REFERENCES

1. Nilsson L, Albrechtsson U, Jonung T, et al. Surgical treatment versus thrombolysis in acute arterial occlusion: a randomized controlled study. *Eur J Vasc Surg.* 1992;6:189–193.
2. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg.* 1994;19:1021–1030.
3. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE Trial. *Ann Surg.* 1994;220:251–268.
4. Graor RA, Risius B, Denny KM, et al. Local thrombolysis in the treatment of thrombosed arteries, bypass grafts, and arteriovenous fistulas. *J Vasc Surg.* 1985;2:406–414.
5. McNamara TO, Bomberger RA. Factors affecting initial and 6 month patency rates after intraarterial thrombolysis with high-dose urokinase. *Am J Surg.* 1986;152:709–712.
6. Endoarterial treatment of acute ischemia of the limbs with urokinase. Italian Cooperative Study (Bologna). *Int Angiol.* 1989;8:53–56.
7. Sicard GA, Schier JJ, Totty WG, et al. Thrombolytic therapy for acute arterial occlusion. *J Vasc Surg.* 1985;2:65–78.
8. Lonsdale RJ, Berridge DC, Earnshaw JJ, et al. Recombinant tissue-type plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis. *Br J Surg.* 1992;79:272–275.
9. Meyerovitz MF, Coldhaber SZ, Reagan K, et al. Recombinant tissue-type plasminogen activator versus urokinase in peripheral arterial and graft occlusions: a randomized trial. *Radiology.* 1990;175:75–78.
10. Weaver FA, Comerota AJ, Youngblood M, et al. Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: results of a prospective randomized trial. The STILE Investigators. Surgery versus Thrombolysis for Ischemia of the Lower Extremity. *J Vasc Surg.* 1996;24:513–523.
11. Ouriel K, Gray B, Clair DG, et al. Complications associated with the use of urokinase and recombinant tissue plasminogen activator for catheter-directed peripheral arterial and venous thrombolysis. *J Vasc Interv Radiol.* 2000; 11:295–298.
12. Swischuk JL, Fox PF, Young K, et al. Transcatheter intraarterial infusion of rt-PA for acute lower limb ischemia: results and complications. *J Vasc Interv Radiol.* 2001;12:423–430.
13. Yenari MA, Palmer JT, Bracci PM, et al. Thrombolysis with tissue plasminogen activator (tPA) is temperature dependent. *Thromb Res.* 1995; 77:475–481.
14. Schwarzenberg H, Muller-Hulsbeck S, Brossman J, et al. Hyperthermic fibrinolysis with rt-PA: in vitro results. *Cardiovasc Intervent Radiol.* 1998;21:142–145.
15. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;26:517–538.
16. Berridge DC, Gregson RH, Hopkinson BR, et al. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and

intra-arterial streptokinase in peripheral arterial thrombolysis. *Br J Surg.* 1991;78:988–995.
17. Mahler F, Schneider E, Hess H, the Steering Committee, Study on Local Thrombolysis. Recombinant tissue plasminogen activator versus urokinase for local thrombolysis of femoropopliteal occlusions: a prospective, randomized multicenter trial. *J Endovasc Ther.* 2001;8:638–647.
18. Braithwaite BD, Buckenham TM, Galland RB, et al. Prospective randomized trial of high–dose bolus versus low–dose tissue plasminogen activator infusion in the management of acute limb ischaemia. *Br J Surg.* 1997;84:646–650.
19. Belli AM. Thrombolysis in the peripheral vascular system. *Cardiovasc Intervent Radiol.* 1998;21:95–101.
20. Braithwaite BD, Birch PA, Poskitt KR, et al. Accelerated thrombolysis with high dose bolus t-PA extends the role of peripheral thrombolysis but may increase the risks. *Clin Radiol.* 1995; 50:747–750.
21. Rao AK, Pratt C, Berke A, et al. Thrombolysis in myocardial infarction (TIMI) trial–phase1: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol.* 1988;11:1–11.
22. Weitz JI. Limited fibrin specificity of tissue-type plasminogen activator and its potential link to bleeding. *J Vasc Interv Radiol.* 1995;6:19S–23S.
23. Verstraete M, Bounameaux H, De Cock F, et al. Pharmacokinetics and systemic fibrinogenolytic effects of recombinant human tissue-type plasminogen activator (rt-PA) in humans. *J Pharmacol Exp Ther.* 1985;235:506–512.
24. Aschoff J, Wever R. Kern und Schale im Heatehaushalt des Menschen. *Naturwissenschaften.* 1958;45:477–481.