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.

Key words: lower limb ischemia, thrombosis, thrombolysis, recombinant tissue plasminogen activator, hyperthermic fibrinolysis, recanalization
lysis\textsuperscript{9,10}; however, there is a higher incidence of major hemorrhagic events with rtPA than urokinase.\textsuperscript{11,12}

Several years ago, two in vitro studies showed that elevated temperature increases the fibrinolytic activity of tissue plasminogen activator.\textsuperscript{13,14} Based on these experimental observations, we designed a prospective non-randomized 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\textsuperscript{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
balloon dilated with or without stent implantation; if the lesion was too long for angio-
plasty, the patient was prepared for semielec-
tive surgery. If there was insufficient clinical improvement after thrombolysis, the patient
went to urgent surgery without awaiting re-
versal of the effects of the thrombolytic ther-
apy. These patients were continued on intra-
venous heparinization, but the rtPA infusions
were terminated.

After thrombolysis and any complementary
procedures, all patients were started on intra-
venous heparin for 48 hours and continued
with ticlopidine for 6 weeks and thereafter
with aspirin for life. Ankle-brachial index mea-
surement 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: ische-
mic classification (viable versus threatened),
symptom duration (≤14 versus >14 days),
and cause (embolism versus thrombosis), as
well as anatomical location (iliac versus in-
frainguinal) and length of the thrombotic oc-
cclusion (≤10 versus >10 cm). Similar tests
were also applied for comparison of the 30-
day amputation-free survival rates and to as-
ss the impact of heating the rtPA on the
thrombolytic outcome (positive versus nega-
tive) 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 be-
tween the groups. Statistical significance was
indicated by p≤0.05.

RESULTS

There was no significant difference between
the groups with regard to demographics; the
classification, duration, and cause of ische-
mia; 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 pa-
tient. A positive thrombolytic outcome was
obtained in 28 (82%) patients: 14 in each
group (p=0.77). Thus, heating of the rtPA bo-
luses did not affect the outcome of the pro-
cedure. However, in patients treated with
heated rtPA, there were statistically signifi-
cant 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. Although the rates of major hemorrhagic events are higher with rtPA than with urokinase, the thrombolytic process with this agent tends to be more rapid. In the only randomized study comparing rtPA to urokinase, 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. This is of utmost importance when prompt revascularization is required (class IIA and, particularly, IIB limb ischemia). 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. 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. 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. Because this rtPA-mediated fibrinogenolytic process is both delayed and prolonged, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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
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