Reteplase with or without Abciximab for Peripheral Arterial Occlusions: Efficacy and Adverse Events

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PURPOSE: To retrospectively evaluate reteplase in thrombolysis of peripheral arterial occlusion (PAO).

MATERIALS AND METHODS: Forty limbs in 36 patients were treated with reteplase (0.5 U/h) with or without abciximab (bolus and 12-hour infusion). Twenty-four occlusions were in bypass grafts and 16 were in native arteries. Nineteen patients were treated with reteplase alone and 21 patients were treated with reteplase and abciximab. Chart review provided data from procedures and follow-up at 30 days and 6 months. Multivariable, analysis of variance, and Student *t* test comparisons of results and complications were performed.

RESULTS: Reteplase infusions averaged 31 hours in duration (range, 12–72 hours). The technical success rate was 80%. The clinical success rates were: immediate, 80%; 30-day, 65%; and 6-month, 45%. Major bleeding complications occurred in 20% of cases and intracranial hemorrhage occurred in 2.5%. The 6-month amputation-free survival rate was 78%. Major, minor, and lack of complications were statistically associated with mean decreases in fibrinogen levels from baseline of 72%, 46%, and 15%, respectively ($P = .000013$). Complications were not associated with length of infusion or use of abciximab ($P = .77$). Patients with grafts accounted for 89% of the major complications (eight of nine; $P = .009$) and had worse clinical success immediately (71%), at 30 days (50%), and at 6 months (21%; $P = .002$, $P = .003$, $P = .00001$).

CONCLUSIONS: There was significant fibrinogen depletion with use of reteplase for PAO. The percent decrease in fibrinogen level correlates with lack of complications and incidence of minor and major complications. Abciximab use did not increase the complication rate. Thrombolysis of grafts is associated with increased incidence of complications and worse outcomes compared with thrombolysis of native arteries.

J Vasc Interv Radiol 2004; 15:557–564

Abbreviations: Gp = glycoprotein, PAO = peripheral arterial occlusion, SVS/ISCVS = Society of Vascular Surgery and International Society of Cardiovascular Surgery

DRUGS used for thrombolysis of peripheral arterial occlusion (PAO) in the past 30 years include streptokinase, urokinase, and alteplase (recombinant tissue plasminogen activator [t-PA]; Activase; Genentech, South San Francisco, CA). Urokinase was the dominant drug until it was removed from the market by the Food and Drug Administration in 1999 (1). The absence of urokinase left t-PA, recombinant t-PA, and the truncated mutant of recombinant t-PA, reteplase (Retavase; Centocor, Malvern, PA), as the only widely available thrombolytic agents (2). Experience with these drugs was limited, but there was rapid development of protocols to treat PAO (3).

During this same time period, there has been interest in the use of glycoprotein (Gp) IIb/IIIa inhibitors in combination with thrombolytic agents to enhance the speed and effectiveness of thrombolysis and maintain patency of vessels after endovascular interventions. Gp IIb/IIIa inhibitors have been used in combination with thrombolysis in the acute coronary syndromes, but few data exist on this combination in the treatment of PAO (4–6). The Gp IIb/IIIa inhibitors available are abciximab (Centocor, Malvern, PA), tirofiban (Merck, West Point, PA), and eptifibatide (Millennium, San Francisco, CA).

In our practice, we have used reteplase as our thrombolytic drug and added the potent Gp IIb/IIIa inhibitor abciximab in more difficult cases. This article presents a retrospective view of our experience with the thrombolytic

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None of the authors have identified a conflict of interest.

DOI: 10.1097/01.RVI.0000127891.54811.02

Table 1
Patient Outcomes on the Society of Interventional Radiology Acute Ischemia Scale (8)

Category	Definition
−1	Ischemia worse (by one category on acute ischemia scale)
0	No change
+1a	Revascularization by thrombolysis alone
+1b	Adjunctive surgery needed, but at lesser level
+1c	Adjunctive endovascular treatment needed

drug reteplase alone or in combination with abciximab in PAO.

MATERIALS AND METHODS

This nonrandomized retrospective study was approved by the hospital investigational review board. Data were compiled from chart review of 40 consecutive patients treated for PAO from January 2000 to December 2001. All patients were referred for acute ischemia of recent onset. The decision whether to use abciximab was based on operator preference. Typically, abciximab was used at the outset for cases with poor flow and prominent ischemia. Abciximab was added at 24 and 48 hours in patients with evidence of recurrent thrombosis. The inclusion and exclusion criteria in use at our institution are as follows.

Inclusion Criteria

1. Patient has given written informed consent before the procedure.
2. Patient has acute ischemia of <7 days duration.
3. Patient is a man or nonpregnant woman ≥18 years of age.
4. An angiogram is available confirming vascular occlusion of a native artery or graft in lower or upper extremity causing claudication or ischemia.

Exclusion Criteria

1. Patient has internal bleeding involving intracranial and retroperitoneal sites or gastrointestinal, genitourinary, or respiratory tracts.
2. Patient has superficial or surface bleeding, observed mainly at vascular puncture and access site or recent surgical site.
3. Patient has known history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, and subacute bacterial endocarditis.
4. Patient, if female, has a positive pregnancy test result.
5. Patient has had a recent stroke or transient ischemic attack or any central nervous system neoplasm, bleeding, arteriovenous malformation, or aneurysm.
6. Patient has had peripheral arterial grafts placed <2 months ago, infected grafts, or grafts not amenable to thrombolytic therapy.
7. Patient has severe uncontrolled hypertension defined as blood pressure ≥180/110 on repeated measurements before the study.
8. Patient has acute leg ischemia classified as ≥III according to the Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ISCVS) scale (7).

Treatment Protocol

All patients had diagnostic angiography of the affected limb performed before initiation of thrombolysis. The occluded artery or graft was entered with a guide wire, and an infusion catheter of appropriate length (various manufacturers) was placed within the clot. Thrombolytic infusion was then initiated. All patients received reteplase infused at a rate of 0.5 U/h (10 U in 500 mL normal saline solution at 25 mL/h). Patients were not given boluses of reteplase. Heparin was not infused during thrombolysis, but a heparin bolus of 3,000–5,000 IU was usually given during catheter manipulation, angioplasty, and stent placement. Abciximab was given as an intravenous bolus of 0.25 mg/kg followed by a 12-hour infusion of 0.125 μg/kg/min. Patients were followed in the intensive care unit. Repeat angiography was performed the next day and every subsequent 24 hours during infusion.

Definitions

Infusion time was rounded to the nearest hour. Technical success was defined as removal of more than 95% of clot from the affected occlusion and distal runoff. Immediate and 30-day clinical success was defined according to the Society of Interventional Radiology (SIR) acute ischemia reporting scale (8) at +1 including subcategories a, b, and c (**Table 1**). Clinical success at 6 months was defined by an SVS/ISCVS outcome score greater than +1 (7). The percent decrease in fibrinogen level was defined as the admission fibrinogen level minus the fibrinogen nadir divided by the admission fibrinogen level. Complications were defined by SIR reporting standards and categorized as major or minor (8). Major complications were defined as procedure-related events within 30 days of the procedure including death, cerebral hemorrhage, myocardial infarction, bleeding requiring transfusion of 2 U of packed red blood cells, or significant clinical event causing increased level of care or premature abandonment of thrombolysis. Minor bleeding complications were defined as hematomas or bleeding not requiring transfusion of packed red blood cells. Patients lost to follow-up were scored a −3 on the outcome scale (7).

Data Analysis

Quantitative and statistical comparisons between the reteplase-alone and reteplase/abciximab groups were made with respect to cardiac risk factors, age, acute ischemia score, chronic ischemia score, technical success, complications, clinical success, and immediate, 30-day, and 6-month outcomes. Cardiac risk factors evaluated included age, coronary artery disease, hypertension, carotid artery disease, hyperlipidemia, chronic obstructive pulmonary disease, smoking, hypercoagulable states, diabetes, and chronic renal failure. Additional comparisons were made based on fibrinogen levels before thrombolysis and at the intraprocedural nadir, admission blood pressure, and whether the ob-

Table 2
Patient Risk Factors

	Reteplase (n = 19)	Reteplase/ Abciximab (n = 21)	P Value
Male sex	15 (79)	12 (57)	.15
Coronary artery disease	13 (68)	10 (48)	.10
Hypertension	11 (58)	13 (62)	.40
Carotid artery disease	1 (5)	1 (5)	.47
Hyperlipidemia	3 (16)	10 (48)	.016*
COPD	5 (26)	4 (19)	.30
Smoking	12 (63)	15 (71)	.294
Hypercoagulopathy	0	1 (5)	.168
AODM	8 (42)	10 (48)	.379
Chronic renal failure	3 (16)	3 (14)	.449
Graft thrombolysis	11 (58)	12 (58)	.401

* Significant intergroup difference.
Note.—Numbers in parentheses are percentages. AODM = adult onset diabetes mellitus; COPD = chronic obstructive pulmonary disease.

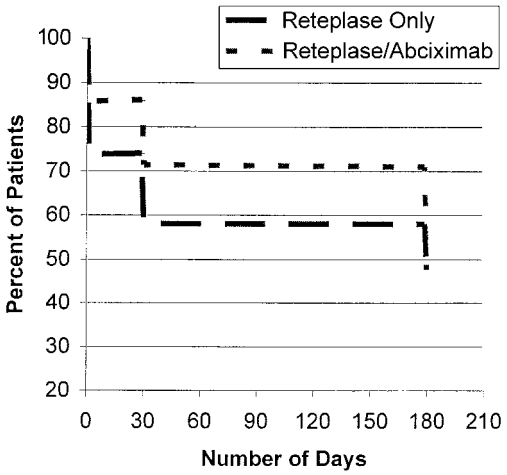

Figure 1. Kaplan-Meier analysis of clinical patency in patients with outcome scores of at least +1. The SEs for treatment with reteplase alone at 0, 30, and 180 days were 0.107, 0.114, and 0.086. The SEs for reteplase and abciximab at 0, 30, and 180 days were 0.068, 0.106, and 0.092.

structed vessel was a native artery or a bypass graft.

Outcomes of thrombolysis were determined as described by the SIR criteria described by Patel et al (8). Acute and chronic ischemia scores described by Rutherford et al (7) for SVS/ISCVS were obtained from chart review of ankle brachial indexes and clinical descriptions of patients. The chronic ischemia scores were used to generate the SVS/ISCVS outcomes scores for immediate, 30-day, and 6-month outcomes. Death and amputation rates were evaluated.

Statistical Analysis

Multivariable selection analysis, symmetric and asymmetric two-sample Student t tests, and analysis of variance were used to evaluate data for statistically significant differences. Kaplan-Meier curves were generated for clinical patency and amputation-free survival.

RESULTS

Technical and Clinical Results

Forty infusions were performed in 36 patients. Two patients had two infusions and one patient had three infusions. Thirty-eight infusions were in lower extremities and two were in upper extremities. Sixteen native artery occlusions and twenty-four graft occlusions were treated. In the 21 limbs treated with abciximab, 13 infusions were started with thrombolysis, six started at 24 hours, and two started at 48 hours.

Demographic and cardiac risk factors are listed in **Table 2**. Acute ischemia levels at the time of thrombolysis initiation were level I in 15% of cases (n = 6), level IIa in 37.5% of cases (n = 15), and level IIb in 47.5% of cases (n = 19). The average reteplase infusion time was 31 hours (SD, 15 hours). Additional endovascular procedures or surgery (not amputation) were required in 68% of patients. Overall, 48% of cases (n = 19) required angioplasty, 13% (n = 5) required stents, and 8% (n = 3) required surgery. In two patients, aspiration embolectomy was used for thrombus that could not be lysed.

Technical and immediate clinical success was achieved in 80% of infusions (n = 32). Clinical success was achieved with thrombolysis alone (+1a) in 25% of cases (n = 10), with adjunctive surgery (+1b) in 5% of cases (n = 2), and with adjunctive endovascular procedure (+1c) in 50% of cases (n = 20). No clinical improvement occurred in 15% of cases (n = 6), and 5% of cases (n = 2) had worsening ischemia (−1).

Long-term follow-up results for immediate, 30-day, and 6-month outcomes were based on the SVS/ISCVS scale from −3 to +3 (7). The clinical success (outcome of at least +1) rates for all patients were 80% immediately, 65% at 30 days, and 45% at 6 months. The Kaplan-Meier analysis of clinical patency is shown in **Figure 1**.

Patients treated with abciximab had increased reteplase infusion times of 36 hours (SD, 18 hours), compared with 25 hours (SD, 9 hours) in the reteplase-only group (P = .008). The patients in the abciximab group showed a trend toward improved technical and early clinical success. Technical and clinical success was achieved in 86% of patients treated with abciximab (18 of 21) and 74% of patients treated with reteplase only (14 of 19). Improved outcomes continued in the patients receiving abciximab (71% vs 48%) at 30 days, but at 6 months, the clinical patency rates were only 48% in patients who received abciximab and 42% in patients who received reteplase only. The differences between the patients who received reteplase only and those who received abciximab did not reach statistical significance with regard to presentation acute ischemia scores, technical success, clinical success, major complications, or immediate, 30-day, and 6-month outcomes (P = .36, P = .177, P = .43, P = .77, P = .26, P = .27, P = .29).

In the subgroup of eight patients who received abciximab at 24–48 hours into their thrombolytic infusion for evidence of poor progression or active recurrent thrombosis, the technical success rate was 100% and clinical success rates were 100% immediately, 100% at 30 days, and 75% (six of eight) at 6 months.

In the group of 24 bypass grafts, 13 had vein grafts, 10 had synthetic grafts, and one had both. The synthetic grafts included five femoropopliteal grafts, two aortobifemoral grafts, two endografts, and one femorofemoral bypass graft. Patients with bypass grafts had a 75% technical success rate (18 of 24), compared with 88% in patients with native artery occlusions. The clinical success rates in bypass grafts were 71% immediately, 50% at 30 days, and 21% at 6 months, compared with 94% immediately, 88% at 30 days, and 81% at 6 months in native arteries (immediate, $P = .002$; 30 days, $P = .003$; 6 months, $P = .00001$).

Complications

Overall, 58% of patients (23 of 40) had no complications, 20% (eight of 40) had minor complications, and 23% (nine of 40) had major complications. The overall rate of major complications caused by bleeding was 20% (eight of 40). The major complication rate was higher because of one patient with respiratory failure requiring intubation. Major bleeding complications included one cerebral hemorrhage with death, one ischemic stroke and death secondary to bleeding and hypotension, one case of hemoptysis, five hematomas requiring transfusion, and one myocardial infarction in a patient with hematoma requiring transfusion. Major complications had a statistically significant correlation with the percent decrease of fibrinogen level ($P = .00003$), lowest fibrinogen level ($P = .000007$), and thrombolysis of bypass grafts versus native arteries ($P = .009$). Major complications were associated with a mean 72% decrease in fibrinogen, minor complications were associated with a mean 46% decrease in fibrinogen, and lack of complications was associated with a mean 15% decrease. A fibrinogen of 100 or less was found in 33% of patients with major complications (three of nine) and in 5% of patients with no or minor complications (two of 31; $P = .024$). The correlation of major complications with fibrinogen level of less than 100 mg/dL was less significant than the correlation with percent decrease in fibrinogen level, and the sample size was inadequate to show statistical significance.

In the subgroup of eight patients who received abciximab at 24–48 hours, there was one major complication (13%), a 50% incidence of minor complications ($n = 4$), and 25% of patients with no complications ($n = 2$). The major complication was a hematoma requiring transfusion.

Patients with grafts had a 33% rate of major complications (eight of 24) whereas patients with native artery occlusion had a 6% rate of major complications (one of 16; $P = .009$). There were major complications in 27% of patients with synthetic grafts (three of 11) and in 38% of patients with vein grafts (five of 13; $P = .29$). Of patients with major complications, 89% (eight of nine) had occluded bypass grafts. All deaths and amputations occurred in patients with bypass grafts. Patients with grafts had a trend toward a greater percent decrease in fibrinogen (44% vs 23% in native arteries), which did not reach statistical significance ($P = .078$). Average infusion times were similar for graft and native artery occlusions, at 34 hours (SD, 17 hours) and 27 hours (SD, 10 hours), respectively ($P = .066$).

Two-sample t tests comparing patients with major complications versus those with no or minor complications demonstrated nonsignificant differences with respect to use of abciximab ($P = .077$), age ($P = .184$), diastolic and systolic blood pressure on admission ($P = .377$ and $P = .313$, respectively), technical success ($P = .134$), infusion time ($P = .39$), and acute ischemia score ($P = .186$). Statistically significant differences were found in percent decrease in fibrinogen level ($P = .00003$), lowest fibrinogen level ($P = .000007$), bypass grafts ($P = .009$), and outcomes immediately ($P = .002$), at 30 days ($P = .0002$), and at 6 months ($P = .0002$).

An analysis of variance was performed on complications (none, minor, and major) versus other variables. Unlike t tests, analysis of variance can find statistically significant differences in all three categories of complications. This analysis showed a significant association of complications with the percent decrease in fibrinogen level ($P = .000013$), bypass grafts ($P = .014$), and outcomes (**Table 3**).

The overall death and amputation rates (outcome grade, −3) were 18% at 30 days (seven of 40) and 23% at 6 months (nine of 40). At 6 months, there were six amputations overall, with amputation rates of 16% in the reteplase-only group (three of 19) and 14% in the reteplase/abciximab group (three of 21). Three patients died during the study. Two of the three deaths resulted from cerebral vascular accidents. One patient in the reteplase-only group had an ischemic stroke and died. The second patient, who received reteplase and abciximab, died of intracranial hemorrhage. A third patient in the reteplase-abciximab group died of unknown causes before the 6-month follow-up. One patient was lost to follow-up at the 6-month interval. The Kaplan-Meier analysis for amputation-free survival is shown in **Figure 2**.

Table 3
Analysis of Complications by Analysis of Variance

Variable Correlated with Complications	*P* Value
Age	.149
Treatment regimen	.502
Technical success	.301
Native artery vs. graft thrombolysis	.014*
Percent decrease in fibrinogen	.000013*
Outcome	
Immediate	.0059*
At 30 days	.00063*
At 6 months	.0027*

* Statistically significant.

Of special interest are the two cases of cerebral vascular accident and death. The first case was in a 68-year-old female ex-smoker with history of carotid disease who presented with grade IIb acute ischemia from occlusion of a Gore-Tex (W.L. Gore & Associates, Flagstaff, AZ) femoral popliteal bypass graft. She received a 16.5-hour infusion of reteplase, which completely thrombolysed her graft. The next day, the patient developed hypotension, had a seizure, and had a nonhemorrhagic stroke and died.

The second patient was a 76-year-old woman with grade IIb/III ischemia on admission from an occluded Gore-Tex (W.L. Gore & Associates) femoropopliteal bypass graft who was recommended for surgery but refused for religious reasons. The patient was treated with 0.5 U/h reteplase for 27

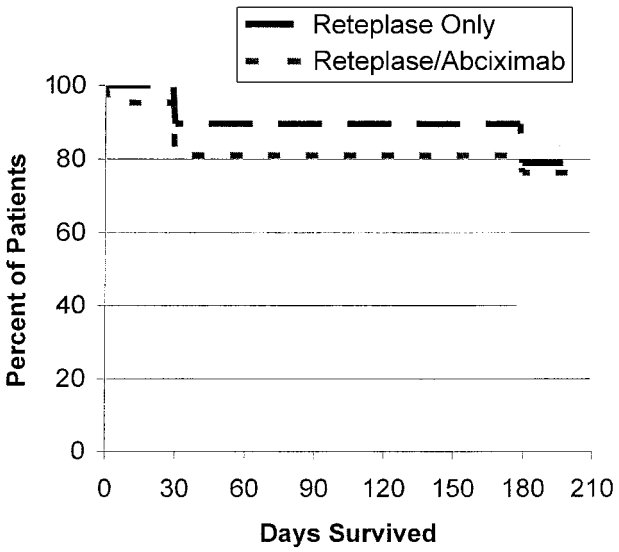

Figure 2. Kaplan-Meier analysis of amputation-free survival. The SEs for treatment with reteplase alone at 0, 30, and 180 days were 0.048, 0.059, and 0.087. The SEs for reteplase and abciximab at 0, 30, and 180 days were 0.034, 0.058, and 0.087.

hours as well as a 0.25-mg/kg bolus of abciximab followed by a 12-hour infusion at 0.125 μg/kg/h. At 27 hours, the patient's neurologic status suddenly changed, and computed tomography revealed a cerebral hemorrhage that led to herniation and death.

DISCUSSION

The most important findings of this study were the complications and their correlation with percent decrease in fibrinogen level. These findings support the idea that fibrinogenolysis of circulating fibrinogen by plasminogen activators contributes to bleeding (9). Another important but unexplained finding was the association of complications with bypass grafts. A final interesting finding was that abciximab did not increase the incidence of complications, but was associated with a trend toward improved immediate and 30-day results and worked well for recurrent thrombosis.

In studies of reteplase for PAO, technical success rates have varied from 70% to 93% (6,10). The clinical success rates are reported to range from 75% to 93% (6,11). Major bleeding complications have been reported to occur between 0 (6) and 19% (12) of cases in which reteplase is used. Our results are comparable to the those in the reported literature in terms of technical success, clinical success, and major bleeding complications. There are insufficient reports on reteplase to evaluate the amputation and death rates. Our results compare well with the findings of a large review of intraarterial thrombolysis versus surgery in which the amputation rates with thrombolysis and surgery were 11% and 27%, respectively, at 6–12 months. The death rates were 8% and 29%, respectively, at 6–12 months (13).

Thrombolysis of occluded grafts has been shown to be worthwhile in thrombotic occlusion less than 14 days old (14,15). In our series, patients with grafts had the lowest technical and clinical success rates and accounted for 89% of major complications (eight of nine) and all amputations and deaths. In the patients with grafts, there was a trend toward greater percent decrease in fibrinogen levels (44% vs 23%; $P = .078$) that cannot be explained, other than possibly by the increased thrombus burden in bypass grafts. Another possible explanation is that the overall medical condition of patients with bypass grafts and the extent of their peripheral vascular disease are likely to be worse than in patients without grafts.

Our data showed an early clinical success rate of 86% patients treated with reteplase and abciximab, versus 74% in the reteplase-only group. The difference did not reach statistical significance. This trend toward improved outcome in the reteplase/abciximab group subsided at 6 months, at which time results were nearly equal between treatment groups. However, the lack of late benefit is a likely result of progression of disease as opposed to lack of effectiveness of abciximab. Our major complication rate was 24% in patients receiving abciximab (five of 21), which is near the high end of the range noted in three other published studies (4–6). However, our major complication rate with reteplase alone was also high at 21% (four of 19), and the difference was not statistically significant. Our complication rate may be related to the high percentage of patients with bypass grafts, in whom the majority of complications occurred.

Thrombolytic Resistance

The use of abciximab resolved the problem of sudden thrombosis during interventions and catheter manipulations we had frequently observed before instituting the use of abciximab. This phenomenon has been best described as "thrombolytic resistance," in which platelet activity causes recurrent thrombosis during thrombolysis (16,17). The Global Use of Strategies to Open Occluded Coronary Arteries III investigators described platelet activity and Gp IIb/IIIa expression to be high in the 12–24 hours after intravenous coronary thrombolysis, especially when reteplase is used (18). This same effect may occur in thrombolysis infusions for PAO. In our patients, we observed the development of castlike thrombi in vessels already partially or completely thrombolysed (**Fig 3**). This recurrent thrombosis would often happen during catheter manipulation or angioplasty after a patient had undergone reteplase infusion for 1–2 days despite previous bolus administration of 3,000–5,000 U heparin. We added abciximab to our reteplase infusions specifically for this problem in eight of 34 patients (24%) not already receiving abciximab at 24 hours or more. These patients were also treated with boluses of heparin of 3,000–5,000 U. All eight cases were technically and clinically successful. There was one major complication of a retroperitoneal hematoma requiring transfusion. This group of patients with signs of

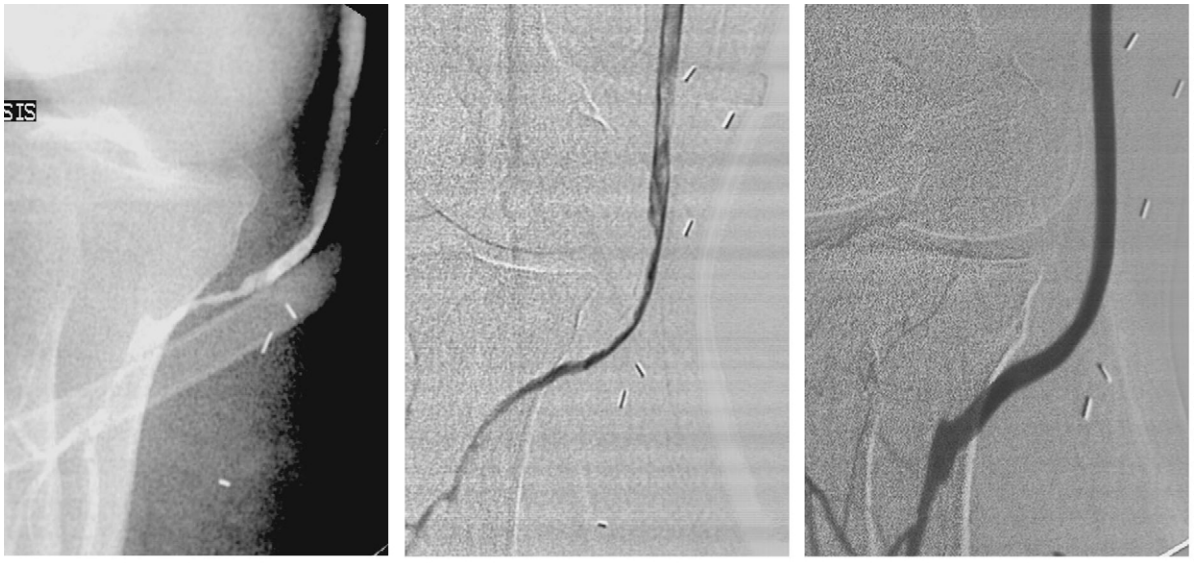

Figure 3. **(a)** Angiogram from 24 hours into reteplase infusion shows some residual thrombus in the distal femoral popliteal bypass graft. **(b)** Angiogram at 48 hours demonstrates castlike thrombus in the femoral popliteal bypass graft that developed on the table during catheter exchange. **(c)** Angiogram at 72 hours after additional treatment with reteplase and abciximab.

recurrent thrombosis on follow-up angiography may be ideal patients for abciximab use.

Bleeding Complications

There has been an increasing number of reports on the use of reteplase for PAO. The theoretic advantage of reteplase compared with alteplase is its reduced fibrin specificity, which should enhance the drug's ability to penetrate thrombus and perhaps increase its safety margin by not binding to and thrombolysing nontarget fibrin plugs that are preventing bleeding throughout the body (12). Our data appear to support another theory that suggests that bleeding complications with plasminogen activators are caused by fibrinogenolysis (9).

In our study, there is an unambiguous association of percent decrease in fibrinogen level with complications. The association of complications with fibrinogen levels has been inconsistent throughout the literature on thrombolysis. The Surgery versus Thrombolysis for Ischemia of the Lower Extremity trial (19) and a smaller study of 32 patients (20) found that complications did correlate with fibrinogen levels with the use of alteplase, whereas another study (21) reporting the use of alteplase found that the fibrinogen level remained greater than 65% of baseline in all patients, including patients with major bleeding complications and intracranial hemorrhage. In other studies involving reteplase for PAO, fibrinogen depletion was not reported to have a significant correlation with complications (6,11,12,22).

Weitz (9) has shown that t-PAs cause fibrinogenolysis by reacting with degradation products of cross-linked fibrin especially the D-dimer noncovalently bound to fragment E known as DD(E), and circulating fibrinogen leading to accumulation of fragment X and bleeding. Weitz (9) and Stewart et al (23) have showed that more fibrin-specific agents caused less fibrinogenolysis than the less fibrin-specific plasminogen activators. Reteplase, being less fibrin-specific than other plasminogen activators, may be particularly susceptible to causing bleeding complications by fibrinogenolysis. It is not clear if the change in fibrinogen level is an adequate measure of the risk of bleeding or degree of fibrinogenolysis.

This current study does not define a specific fibrinogen level at which bleeding complications can be predicted to occur. Based on our data, it may be prudent to limit or stop reteplase infusions when a 70% or greater decrease in fibrinogen level occurs and when fibrinogen levels are less than 100. Transfusion of cryoprecipitate will increase fibrinogen levels and may help control bleeding (24,25).

Reducing the rate of thrombolytic infusion has been studied as a method of reducing complications. Castaneda et al (26), in a recent report, described decreasing bleeding complications by 59% (from 13.3% to 5.4%) with a mild decrease in thrombolytic success (86.7% vs 83.8%) when administering reteplase at 0.25 U/h rather than 0.5 U/h. Other studies of reteplase in PAO have used doses ranging from 0.5 U/h to 2.0 U/h (6,10–12,22). One study found a lower thrombolysis rate of 66% with use of 0.5 U/h compared with 100% with use of 1.0 U/h (11). This latter report notwithstanding, it would appear that the use of a lower infusion rate might prove a useful strategy to lower the incidence of complications.

A concern related to infusion rate is the ideal infusion concentration. Although this has not been studied in humans, Bookstein and Bookstein (27) reported the ideal reteplase concentration for thrombolysis in a rabbit model as 0.02 U/mL, which is the concentration we delivered by diluting 10 U reteplase in 500 mL of normal saline solution.

Abciximab

There are few reports of the combination of reteplase and abciximab for treatment of PAO in the literature (6,17). The doses, safety, and efficacy of these drugs in PAO have not been established. We first began to use t-PA and reteplase when urokinase was removed from the market by the Food and Drug Administration in 1999 (1). We noted on several occasions that thrombosis would occur suddenly in vessels and around catheters during interventions or catheter manipulations after an initial overnight infusion of thrombolytic drug. This phenomenon has been described as "thrombolytic resistance" by Cannon et al (16), who have suggested attacking the fibrin, thrombin, and platelet components of thrombus with use of thrombolytic drugs, heparin, and Gp IIb/IIIa inhibitors, respectively. We became interested in treating these thromboses with a Gp IIb/IIIa antagonist with or without bolus administration of heparin. We found that the Gp IIb/IIIa inhibitors seemed to work well for our patients and started adding it to our treatment of acute PAO in cases of recurrent thrombosis and in more complex cases with poor blood flow.

Thrombolysis in Peripheral Artery Occlusion with Abciximab

The combination of thrombolytic drugs and abciximab for the treatment of PAO has been reported in three studies (4–6) in a total of 79 patients. All three studies reported high clinical success rates of 93%–100%. In two small studies of 14 and 15 patients, there were no major bleeding complications (4,6). The largest study to our knowledge to date was a randomized pilot study of urokinase alone versus urokinase with abciximab (5). In this study, thrombolysis was faster, there was an improved amputation-free survival rate, and there was a higher major complication rate (8%) in the urokinase/abciximab group.

Reports of abciximab in the coronary circulation have described improved rate and extent of thrombolysis (28) and allowed a decrease in the dose of reteplase with equal (29) or improved results (30). Complication rates have been described as lower (31) and higher (29) in the coronary circulation even when using reduced doses of thrombolytic drugs. Abciximab with urokinase has been reported to safely improve thrombolysis in the cerebral circulation without causing increased bleeding (32,33). Although not evaluated in our study, it would be interesting to evaluate reduction of the doses of thrombolytic drugs when used in combination with abciximab in the peripheral circulation.

Abciximab is known to cause thrombocytopenia in 3%–5% of patients. In this series, we had no cases of thrombocytopenia. A recent article (34) describes a marked increase in thrombocytopenia to 24% when abciximab is combined with clopidogrel 300 mg. The same authors found no increase in the incidence of thrombocytopenia with clopidogrel 75 mg or ticlopidine 250 or 500 mg.

Heparin

The role of heparin with the t-PA–derived drugs alteplase and reteplase has not been clearly defined (3,17). There are data to suggest that heparin promotes thrombolysis when used with reteplase (12,16). Reducing the heparin dose and lowering the therapeutic range of partial thromboplastin time has been shown to reduce bleeding complications in coronary thrombolysis (16). In a study comparing alteplase with reteplase in PAO, McNamara et al (22) found a 76% rate of significant bleeding in patients treated with alteplase and heparin (13 of 17) and no bleeding complications in patients treated with reteplase and heparin. Ouriel et al (12) reported faster thrombolysis and no increase in bleeding with use of reteplase and heparin infusion of 800 IU/h of in a small number of patients. During the time of this study, we infused heparinized saline solution (2,000 IU/L) through the arterial sheath but did not use heparin infusions. As noted earlier, the use of heparin infusions may beneficial and may have reduced our incidence of thrombolytic resistance.

Study Limitations

This study is limited by being a nonrandomized, retrospective analysis in a small series of patients, and as such it raises more questions than it answers. As noted earlier, there have been some interesting findings that may support evolving theories on the pharmacology of reteplase and abciximab. The study does amplify many of the concerns about the safety of the use of plasminogen activators in the treatment of acute PAO and may suggest directions for further investigation.

Future prospective studies might include the use of more fibrin-specific thrombolytic agents with and without Gp II/IIIa inhibitors, focusing on safety and efficacy. Razavi et al (35) recently noted that the number of patients required to show superiority of specific thrombolytic drugs is too high (in the tens of thousands) to be practically achieved in PAO. Perhaps the best avenue of investigation is to more thoroughly understand the biology behind thrombolysis and bleeding at unintended sites.

CONCLUSION

In our experience, reteplase is capable of causing significant fibrinogen depletion during thrombolytic infusion for PAO. There was a statistically significant association between complications (major, minor, or none) and the percent decrease in fibrinogen level, which may allow stratification of the risk of bleeding during thrombolytic infusion with reteplase. Calculation of the percent decrease in fibrinogen level may be useful in patients undergoing thrombolysis with reteplase.

The use of abciximab with reteplase in the treatment of PAO showed a trend toward improved early results that did not persist at the 6-month interval. The use of abciximab did not significantly increase complications in our patients even though infusions were longer as a result of the cases being selected for poor flow and recurrent thrombosis. Regardless of treatment method, patients with grafts have significantly higher complication rates and poorer outcomes. The finding of recurrent thrombosis or thrombolytic resistance with reteplase and its successful treatment with abciximab was interesting and may warrant further investigation.

References

1. Hartnell GG, Gates J. The case of Abbokinase and the FDA: the events leading to the suspension of Abbokinase supplies in the United States. J Vasc Interv Radiol 2000; 11:841–847.

2. Gates J, Hartnell GG. When urokinase was gone: commentary on another year of thrombolysis without urokinase. J Vasc Interv Radiol 2004; 15:1–5.
3. Semba CP, Murphy TP, Bakal CW, Calis KA, Matalon TA. Thrombolytic therapy with use of alteplase (rt-PA) in peripheral arterial occlusive disease: review of the clinical literature. The Advisory Panel. J Vasc Interv Radiol 2000; 11:149–161.
4. Tepe G, Schott U, Erley CM, Albes J, Claussen CD, Duda SH. Platelet glycoprotein IIb/IIIa receptor antagonist used in conjunction with thrombolysis for peripheral arterial thrombosis. AJR Am J Roentgenol 1999; 172:1343–1346.
5. Duda SH, Tepe G, Luz O, et al. Peripheral artery occlusion: treatment with abciximab plus urokinase versus with urokinase alone—a randomized pilot trial (the PROMPT Study). Platelet Receptor Antibodies in Order to Manage Peripheral Artery Thrombosis. Radiology 2001; 221:689–696.
6. Drescher P, Crain MR, Rilling WS. Initial experience with the combination of reteplase and abciximab for thrombolytic therapy in peripheral arterial occlusive disease: a pilot study. J Vasc Interv Radiol 2002; 13:37–43.
7. Rutherford R, Baker J, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997; 26: 517–538.
8. Patel N, Sacks D, Patel RI, et al. SCVIR reporting standards for the treatment of acute limb ischemia with use of transluminal removal of arterial thrombus. J Vasc Interv Radiol 2001; 12:559–570.
9. Weitz JI. Limited fibrin specificity of tissue-type plasminogen activator and its potential link to bleeding. J Vasc Interv Radiol 1995; 6(suppl):19S–23S.
10. Tepe G, Luz O, Hahn U, et al. Pulsed spray lysis with reteplase in peripheral arterial occlusions—technique and initial results. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2000; 172:780–784. [German]
11. Davidian MM, Powell A, Benenati JF, Katzen BT, Becker GJ, Zemel G. Initial results of reteplase in the treatment of acute lower extremity arterial occlusions. J Vasc Interv Radiol 2000; 11: 289–294.
12. Ouriel K, Katzen B, Mewissen M, et al. Reteplase in the treatment of peripheral arterial and venous occlusions: a pilot study. J Vasc Interv Radiol 2000; 11:849–854.
13. Diffin DC, Kandarpa K. Assessment of peripheral intraarterial thrombolysis versus surgical revascularization in acute lower-limb ischemia: a review of limb-salvage and mortality statistics. J Vasc Interv Radiol 1996; 7:57–63.
14. Goh RH, Sniderman KW, Kalman PG. Long-term follow-up of management of failing in situ saphenous vein bypass grafts using endovascular intervention techniques. J Vasc Interv Radiol 2000; 11:705–712.
15. Greenberg RK, Ouriel K. A multimodal approach to the management of bypass graft failure. Vasc Med 1998; 3:215–220.
16. Cannon CP. Overcoming thrombolytic resistance: rationale and initial clinical experience combining thrombolytic therapy and glycoprotein IIb/IIIa receptor inhibition for acute myocardial infarction. J Am Coll Cardiol 1999; 34:1395–1402.
17. Benenati J, Shlansky-Goldberg R, Meglin A, Seidl E. Thrombolytic and antiplatelet therapy in peripheral vascular disease with use of reteplase and/or abciximab. The SCVIR Consultants' Conference; May 22, 2000; Orlando, FL. Society for Cardiovascular and Interventional Radiology. J Vasc Interv Radiol 2001; 12:795–805.
18. Gurbel PA, Serebruany VL, Shustov AR, et al. Effects of reteplase and alteplase on platelet aggregation and major receptor expression during the first 24 hours of acute myocardial infarction treatment. GUSTO-III Investigators. Global Use of Strategies to Open Occluded Coronary Arteries. J Am Coll Cardiol 1998; 31:1466–1473.
19. STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. Ann Surg 1994; 220:251–266.
20. Meyerovitz MF, Goldhaber 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.
21. Bero CJ, Cardella JF, Reddy K, et al. Recombinant tissue plasminogen activator for the treatment of lower extremity peripheral vascular occlusive disease. J Vasc Interv Radiol 1995; 6:571–577.
22. McNamara TO, Dong P, Chen J, et al. Bleeding complications associated with the use of rt-PA versus r-PA for peripheral arterial and venous thromboembolic occlusions. Tech Vasc Interv Radiol 2001; 4:92–98.
23. Stewart RJ, Fredenburgh JC, Leslie BA, Keyt BA, Rischke JA, Weitz JI. Identification of the mechanism responsible for the increased fibrin specificity of TNK-tissue plasminogen activator relative to tissue plasminogen activator. J Biol Chem 2000; 275:10112–10120.
24. Sane DC, Califf RM, Topol EJ, Stump DC, Mark DB, Greenberg CS. Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. Ann Intern Med 1989; 111:1010–1022.
25. Marder VJ. Bleeding complications of thrombolytic treatment. Am J Hosp Pharm 1990; 47(suppl):S15–S19.
26. Castaneda F, Swischuk JL, Li R, Young K, Smouse B, Brady T. Declining-dose study of reteplase treatment for lower extremity arterial occlusions. J Vasc Interv Radiol 2002; 13:1093–1098.
27. Bookstein JJ, Bookstein FL. Pulse-spray thrombolysis with reteplase: optimization and comparison with tPA in a rabbit model. J Vasc Interv Radiol 2001; 12:1319–1324.
28. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000; 101:2788–2794.
29. Topol EJ. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001; 357:1905–1914.
30. Antman EM, Gibson CM, de Lemos JA, et al. Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14. The Thrombolysis in Myocardial Infarction (TIMI) 14 Investigators. Eur Heart J 2000; 21:1944–1953.
31. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. Circulation 1999; 99:2720–2732.
32. Kwon OK, Lee KJ, Han MH, Oh CW, Han DH, Koh YC. Intraarterially administered abciximab as an adjuvant thrombolytic therapy: report of three cases. AJNR Am J Neuroradiol 2002; 23:447–451.
33. Lee DH, Jo KD, Kim HG, et al. Local intraarterial urokinase thrombolysis of acute ischemic stroke with or without intravenous abciximab: a pilot study. J Vasc Interv Radiol 2002; 13:769–774.
34. Dillon WC, Eckert GJ, Dillon JC, Ritchie ME. Incidence of thrombocytopenia following coronary stent placement using abciximab plus clopidogrel or ticlopidine. Cathet Cardiovasc Intervent 2000; 50:426–430.
35. Razavi MK, Lee DS, Hofmann LV. Catheter-directed thrombolytic therapy for limb ischemia: current status and controversies. J Vasc Interv Radiol 2004; 15:13–23.