

Tenecteplase in Acute Lower-leg Ischemia: Efficacy, Dose, and Adverse Events

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PURPOSE: To prospectively evaluate tenecteplase (TNK) for thrombolysis in acute lower-limb ischemia.

MATERIALS AND METHODS: Forty-three consecutive limbs in 37 patients (15 male, 22 female) were treated for acute lower-limb ischemia. Group 1 included 22 limbs treated with TNK infusion of 0.25 mg/h and group 2 included 21 limbs treated with TNK at 0.125 mg/h. Technical success was defined by 95% clearing of thrombus, and clinical success was defined by Society of Interventional Radiology category for acute ischemia of +1. Complications were ranked by severity and relation to TNK administration. Logistic regression, Student *t* test, and analysis of variance were performed.

RESULTS: TNK infusions averaged 24 hours in duration (SD, 13 h), with means of 20 hours in group 1 and 27 hours in group 2 ($P = .071$). Technical success was achieved in 84% of limbs (36 of 43): 82% in group 1 (18 of 22) and 86% in group 2 (18 of 21; $P = .827$). The SIR ischemia category improved (ie, +1) in 86% of limbs (37 of 43), stayed the same (ie, category 0) in 12% of limbs (five of 43), and worsened (ie, -1) in 2% of limbs (one of 43). TNK-related complications were seen in 12% of limbs ($n = 5$) and were correlated with percentage decrease in fibrinogen level, initial TNK bolus, and abciximab administration ($P = .001$, $P < .001$, and $P = .036$, respectively). Initial TNK boluses of 1.5 mg or less were associated with fewer complications than boluses of 3–5 mg ($P = .045$). The percentage decrease in fibrinogen level in group 1 was 23% (SD, 29%), compared with 7% in group 2 (SD, 20%; $P = .045$). There was a 7% incidence of major bleeding complications ($n = 3$) and no intracranial hemorrhages.

CONCLUSIONS: Treatment of acute lower-limb ischemia with TNK infusion at 0.25 mg/h and 0.125 mg/h is associated with similar success and complication rates. TNK-related complications correlated with initial TNK bolus, abciximab treatment, and percent decrease in fibrinogen level. The initial TNK bolus dose should be limited to 1.5 mg.

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Abbreviations: ANOVA = analysis of variance, TNK = tenecteplase, tPA = tissue plasminogen activator

TENECTEPLASE (TNK; Genentech, South San Francisco, CA) is a recombinant DNA thrombolytic agent approved for treatment of acute myocardial infarction. TNK is made by genetic mutation of human tissue plasminogen activator (tPA) at the T, N,

and K domains. The changes have created a drug with a longer half-life of 22 minutes (T domain), a 14-fold increase in fibrin specificity and a twofold improvement in effectiveness in arterial thrombolysis (N domain), an 80-fold increase in resistance to plasminogen activator inhibitor (K domain), and decreased fibrinogen depletion (1–3). The clinical superiority from these changes has not been demonstrated in thrombolytic infusions for acute lower-limb ischemia.

TNK has been found to have an improved safety profile compared with tPA in the treatment of acute myocardial infarction (4), specifically a 22% relative reduction in major bleeding and transfusion. The demon-

strated lower bleeding complications of TNK in acute myocardial infarction might also provide lower incidences of bleeding complications during treatment for acute lower-limb ischemia. Early reports of TNK use for acute limb ischemia have been published and demonstrated clinical success rates of 73%–88% in patients with peripheral arterial occlusive disease treated with an infusion dose of 0.25 mg/h or 0.5 mg/h (5–8). The ideal dose for TNK infusion has not been established. We initially used a dose of 0.25 mg/h as described in published reports (6,8) and then empirically chose to reduce the infusion dose by half to 0.125 mg/h. In this report, we compare our experiences with the ad-

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Table 1
Patient Population

Characteristic	Group 1 (n = 22)	Group 2 (n = 21)	P Value
Age (y)	55	60	.647
Male sex	7 (32)	8 (38)	.748
Grafts	16 (73)	11 (52)	.177
Graft length (cm)	22	20	.652
Graft location*			—
Iliac	9 (41)	9 (43)	
Femoropopliteal	14 (64)	13 (62)	
Distal	4 (18)	6 (29)	

* More than one possible location per patient.

Note.—Numbers in parentheses are percentages.

ministration of TNK at bolus doses of 0.25 mg/h and 0.125 mg/h.

MATERIALS AND METHODS

The hospital investigational review board approved this nonrandomized prospective study. Data were obtained from 43 consecutive limbs in 37 patients treated for peripheral artery occlusive disease from March 2003 to March 2005. All patients were referred for acute ischemia of recent onset (<14 days). The first 22 limbs were treated with TNK infusion at a rate of 0.25 mg/h (group 1) and the second group of 21 limbs received TNK at an infusion rate of 0.125 mg/h (group 2). The lower infusion dose in group 2 was approved as a protocol change by the hospital investigational review board.

The average ages of patients were 55 years (SD, 13 y) in group 1 and 60 years (SD, 14 y) in group 2, which were not significantly different ($P = .185$). Overall, thrombolysis was performed in 15 native arteries (35%), 25 bypass grafts (58%), and three previously stent-implanted arteries (7%), and there was no statistically significant difference in the number of grafts treated in each group ($P = .254$).

The patient populations for groups 1 and 2 were similar in terms of age, sex, grafts, lesion length, and lesion location (Table 1). Cardiovascular risk factors were also similar (Table 2).

Inclusion and Exclusion Criteria

To be included in the study, patients were required to sign a written informed consent form before the procedure, have acute ischemia of less than 14 days' duration, be at least 18

years of age, and have angiographically confirmed vascular occlusion of a native artery or graft in the lower or upper extremity causing claudication or ischemia.

Patients were excluded in cases of internal bleeding involving intracranial and retroperitoneal sites or gastrointestinal, genitourinary, or respiratory tracts; superficial or surface bleeding observed mainly at the vascular puncture and access site or recent surgical site; known history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis; pregnancy; recent stroke or transient ischemic attack or any central nervous system neoplasm, bleeding, arteriovenous malformation, or aneurysm; peripheral arterial graft placement less than 2 months earlier, infected grafts, or inability to undergo thrombolytic therapy; severe uncontrolled hypertension defined by blood pressure of 180/110 mm Hg or greater on repeated measurements before the study; and acute leg ischemia of class III or worse according to the Society of Vascular Surgery and International Society of Cardiovascular Surgery scale for acute leg ischemia (4).

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 before thrombolytic infusion was initiated. Patients in group 1 received TNK infused at a rate of 0.25 mg per

hour (5 mg in 500 mL normal saline solution at 25 mL/h). Patients in group 2 received TNK infused at a rate of 0.125 mg/h (5 mg in 1,000 mL normal saline solution at 25 mL/h). Other than the infusion dose, there were no differences in the treatment protocol between groups 1 and 2. Optional boluses of 1–5 mg TNK (0.25 mg/mL) were given before infusion. Heparinized saline solution or standard heparin (25,000 U in 250 mL 5% dextrose in water) at a subtherapeutic rate (600–800 U/h) was infused into sheaths during thrombolysis. Heparin boluses of 3,000–5,000 IU were usually given during catheter manipulation, angioplasty, and stent placement. Abciximab, when used, was given as an intravenous bolus of 0.25 mg/kg followed by a 12-hour infusion of 0.125 μ g/kg/min. Abciximab was used at operator discretion in patients who showed signs of acute thrombosis during angiography. Patients were followed in the intensive care unit. Repeat angiography was performed the next day and every 24 hours subsequently during infusion.

The patients were followed for additional events through completion of their hospitalization and the next 30 days. Additional follow-up to ascertain death and limb amputation was performed at 30 days and 6 months.

Definitions

Acute ischemia scores as described by Rutherford and the Society of Vascular Surgery and International Society of Cardiovascular Surgery (4) were obtained by physical and Doppler imaging examinations (9). Infusion time was rounded to the nearest hour.

Technical success was defined as removal of more than 95% of clot from affected occlusion and distal runoff. Clinical success was assessed according to the SIR acute ischemia reporting scale (10) and defined by a result of +1 on the SIR ischemia scale (including subcategories a, b, and c; Table 3).

Percent decrease in fibrinogen level was defined as the admission fibrinogen level minus the fibrinogen nadir divided by the admission fibrinogen level.

Complications were ranked on a scale of 1–3 as mild, moderate, or severe (Table 4). A severe complication was defined as a procedure-related

Table 2
Cardiovascular Risk Factors

Risk Factor	Group 1 (n = 22)	Group 2 (n = 21)	P Value
Coronary artery disease	8 (36)	10 (47)	.860
Smoking	18 (81)	15 (71)	.475
Hypertension	13 (59)	15 (71)	.712
Hyperlipidemia	11 (50)	10 (47)	.997
Diabetes	7 (32)	7 (33)	.950
Chronic renal failure	3 (14)	5 (24)	.331
Chronic obstructive pulmonary disease	2 (9)	3 (14)	.375
Carotid artery disease	2 (9)	3 (14)	.375

Note.—Numbers in parentheses are percentages.

Table 3
SIR Acute Ischemia Scale

SIR Acute Limb Ischemia Scale				
Score	Description	Total	Group 1	Group 2
-1	Worsening ischemia	1 (2)	1 (5)	0 (0)
0	No improvement	5 (12)	3 (14)	2 (10)
+1a	Improvement with thrombolysis alone	5 (12)	2 (9)	3 (14)
+1b	Improvement with thrombolysis and surgery	3 (7)	2 (9)	1 (5)
+1c	Improvement with thrombolysis and endovascular procedure	29 (67)	14 (64)	15 (71)

Note.—There was no significant difference among groups.

event within 30 days of the procedure, including death, cerebral hemorrhage, myocardial infarction, or amputation. A moderate complication was defined as a procedure-related event that required an additional level of care. A mild complication was defined as an event requiring treatment but not changing the level of care.

A major bleeding complication was defined as a bleeding complication rated as moderate or severe as described earlier or requiring discontinuation of a thrombolysis procedure.

The relationship of each complication to the drug was ranked on a scale of 1–4 as none, remote, possible, and probable (Table 4). The complication outcomes were ranked on a scale of 1–5 as resolved, improved, unchanged, worse, or death.

Data Analysis

Quantitative and statistical comparisons between the TNK 0.25 mg/h group and the TNK 0.125 mg/h group

were made with respect to all collected data. Four main variable groups were used for statistical analysis and include main outcome variables, cardiac risk factors, drug-related variables, and a combination of laboratory and lesion characteristics variables.

Main outcome variables were defined as technical success, clinical success, SIR outcome criteria, complications, major bleeding complications, and 30-day and 6-month death and amputation rates. Cardiac risk factors included age, sex, smoking history, hypertension, hyperlipidemia, adult-onset diabetes mellitus, coronary artery disease, chronic renal failure, chronic obstructive pulmonary disease, and carotid artery disease (Table 2). For data analysis, these risk factors were rated as present or absent. Drug-related variables were use of heparin boluses, abciximab, TNK infusion dose, TNK infusion time, TNK bolus dose, and total TNK dose (infusion dose plus bolus dose). Laboratory variables included preprocedural an-

kle-brachial index, postprocedural ankle-brachial index, prothrombin time (maximum value measured per 12-hour period), preprocedural fibrinogen level, fibrinogen nadir (measured each 12 hours), and percent decrease in fibrinogen level. Lesion characteristics were lesion length and whether the occluded vessel was a native artery or bypass graft.

Statistical Analysis

Summary statistics, logistic regression analysis, symmetric and asymmetric Student *t* test, and analysis of variance analysis (ANOVA) were used to evaluate for statistically significant differences between groups 1 and 2 and among variables (version 8.1; Medcalc, Mariakerke, Belgium).

RESULTS

TNK infusions averaged 24 hours \pm 14 in duration overall, 20 hours \pm 12 in group 1, and 27 hours \pm 14 in group 2. However, the difference in infusion times between the two groups did not reach statistical significance ($P = .071$). The average infusion doses were 5.02 mg in group 1 and 3.43 mg in group 2. TNK boluses were pulsed into the occlusions of 36 limbs (84%). TNK boluses ranged from zero to 5 mg (0.25 mg/mL) and averaged 1.5 mg \pm 1.2. In group 1, TNK boluses averaged 1.68 mg (SD, 1.48), and in group 2, TNK boluses averaged 1.24 mg (SD, 0.77), without a significant difference between groups ($P = .224$). The average total doses (bolus dose plus infusion dose) were 6.71 mg in group 1 and 4.67 mg in group 2. The infusion dose and total dose were significantly greater in group 1 than in group 2 ($P = .043$ and $P = 0.018$). These and other drug-related parameters are summarized in Table 5.

Heparin infusions were purposely subtherapeutic during thrombolysis, even though, overall, 28 limbs (65%) received heparin boluses of 3,000–5,000 IU in the angiography suite. In group 1, 55% received heparin boluses, versus 76% in group 2 ($P = .224$). The average maximum partial thromboplastin time was 38 seconds in group 1 and was significantly longer in group 2 at 59 seconds ($P = .025$). Seven limbs (16%) received abciximab as a 0.25- μ g/kg bolus and a

Table 4
Complications Ranked by Severity

Rank	Event	Treatment	Relation to TNK	Abciximab Used*	TNK Bolus (mg)*	Decrease in Fibrinogen (%)*	Nadir Fibrinogen Level during Thrombolysis (mg/dL)
Group 1							
1	Fibrinogen decrease	Blood products	Probable	No	5	82	64
1	Embolus	Other	None	No	1.5	15	330
1	PTA; ruptured graft	Other	None	No	0	18	329
3	Hematemesis	Stop TNK	Probable	Yes	5	64	151
3	Level III ischemia	Stop TNK and other treatment	Possible	No	1.5	0	234
3	Compartment syndrome	Stop TNK	None	No	0.5	30	275
Group 2							
1	Allergic reaction	Other drug treatment	None	No	0	7	291
1	Dissection	Other	None	Yes	0.5	26	418
2	Gastrointestinal bleeding	Blood products	Probable	Yes	3	32	389
2	Late hematoma	Blood products	None	No	0	-6	424
3	Repair of brachial artery puncture	Other	Possible	Yes	1.5	-55	620

* Significant association with TNK-related complications by ANOVA.

Note.—PTA = percutaneous transluminal angioplasty. All adverse events were resolved.

12-hour infusion of 0.125 mg/kg/h. A significant majority of these limbs (86%; six of seven) were in group 2 ($P = .039$).

Technical success was achieved in 84% of limbs overall (36 of 43), with an 82% success rate in group 1 and an 86% success rate in group 2 ($P = .827$; **Table 6**). The average ankle-brachial indexes was 0.34 before thrombolysis and 0.70 after thrombolysis ($P = .0001$). Clinical success was achieved in 82% of patients in group 1 and in 90% of patients in group 2 ($P = .422$). Outcome measures are described in **Table 6**. The SIR scale for results of acute limb ischemia (10) showed an improvement (ie, +1) in 86% of limbs (37 of 43), stayed the same (ie, 0) in 12% of limbs (five of 43), and worsened (ie, -1) in 2% of cases (one of 43). The breakdown of results into SIR subcategories by group is given in **Table 3**.

Ten limbs (13%) had thrombolysis with TNK and no additional procedures; five of these cases (50%) had technical and clinical success (SIR category +1a). Additional endovascular procedures were required in 30 of 43 limbs (70%), 29 of which had a clinically successful outcome. Overall, therefore, 67% of limbs (29 of 43) were classified as showing SIR category +1c improvement: 47% were treated with angioplasty ($n = 20$), 30% received a

Table 5
Comparison of Drug-related Parameters

Parameter	Group 1 ($n = 22$)	Group 2 ($n = 21$)	P Value
Mean TNK infusion time SD (h)	20 ± 12	27 ± 14	.071
TNK infusion dose (mg)	5.02	3.43	.043*
TNK bolus (mg)	1.68	1.24	.224
TNK total dose (mg)	6.71	4.67	.018*
Patients who received heparin bolus (%)	55	76	.224
Average maximum PTT (sec)	38	59	.025*
Patients who received Abciximab (%)	5	29	.039*
Fibrinogen level before treatment (mg/dL)	359	435	.035*
Fibrinogen nadir (mg/dL)	272	400	.001*
Mean decrease in fibrinogen level SD (%)	23 ± 29	7 ± 20	.045*

* Statistically significant difference on Student t test.

Note.—PTT = partial thromboplastin time.

Table 6
Outcome Measures

Outcome	Group 1 ($n = 22$)	Group 2 ($n = 21$)	P Value
Technical success	18 (82)	18 (86)	.736
Clinical success	18 (82)	19 (90)	.422
Ankle-brachial index			
Before procedure	0.36	.032	.685
After procedure	0.69	0.71	.838
Major bleeding episode	1 (5)	2 (10)	.537
Death and/or amputation at 6 months	1 (5)	3 (14)	.290

Note.—Values in parentheses are percentages.

stent ($n = 13$), 5% were treated with aspiration embolectomy ($n = 2$), and 12% were treated with pharmacomechanical thrombolysis ($n = 5$). Three limbs required surgery to complete successful thrombolysis (SIR category +1b) and these cases included a fasciotomy for compartment syndrome, a jump revision of a femoral popliteal bypass graft, and thromboendarterectomy with patch angioplasty of the common femoral artery.

Complications occurred in 26% of limbs overall (11 of 43), with a 27% incidence in group 1 ($n = 22$) and a 24% incidence in group 2 ($n = 5$; $P = .800$). Overall, complications were associated with increased age and use of abciximab (logistic regression, $P = .043$ and $P = 0.044$). ANOVA showed only a trend toward increased complications with age, with a mean patient age of 64 years in limbs with complications and a mean age of 55 years in limbs without complications ($P = .077$). ANOVA showed that 57% of limbs treated with abciximab had complications ($n = 4$), compared with 19% of those that were not treated ($n = 7$; $P = .037$).

The complications ranked by severity showed that, overall, 74% of limbs ($n = 32$) had no complications, 12% had mild complications ($n = 5$), 5% had moderate complications ($n = 2$), and 9% had severe complications ($n = 4$). On ANOVA, complication severity had no significant correlation with cardiovascular risk factors, main outcome variables, drug-related variables, or laboratory variables. **Table 4** shows complications by group ranked by severity, treatment, relationship to TNK, and outcome of complication.

Complications, when rated as to the likelihood of TNK as a causative factor (ie, none, remote, possible, probable), exhibited significant correlations on ANOVA with initial TNK bolus, use of abciximab, percent decrease in fibrinogen level, and major bleeding ($P < .001$, $P = .036$, $P = .001$, and $P = .004$, respectively), but not with TNK infusion time or total dose of TNK ($P = .279$ and $P = .075$). The average TNK bolus was 1.4 mg in 32 patients with no complications, 0.5 mg in six patients with complications not related to TNK, 1.5 mg in two patients with complications possibly related to TNK, and 4.3 mg in three patients with complications probably related to

TNK ($P < .001$). There were no patients with complications classified as remotely related to TNK. Similarly, 32 limbs with no complications had a 13% decrease in fibrinogen level, six limbs with complications with no relation to TNK had a 15% decrease in fibrinogen level, two limbs with possible relation to TNK had a 28% increase in fibrinogen level (fibrinogen increased 56% in one of two patients in this group), and three limbs with probable relation to TNK had a 59% decrease in fibrinogen level ($P = .001$).

The finding of a relationship between TNK bolus and TNK-related complications prompted further analysis to discover if there was a TNK bolus that was tolerated without a significant increase in complications. Findings of an ANOVA of all complications versus TNK boluses ranked from zero to 5 mg in 0.5-mg increments were not statistically significant, probably as a result of small sample sizes ($P = .052$). However, TNK boluses of 1.5 mg or less were well-tolerated, with a 22% overall complication rate (eight of 36), whereas TNK boluses of 3–5 mg had a 75% complication rate (three of four; student *t* test, $P = .025$). Of note, only two of eight limbs in the 1.5-mg bolus group had complications ranked as possibly TNK-related, whereas all three of four limbs in the 3–5-mg bolus group were ranked as probably related to TNK.

There were three major bleeding complications (7%), with a 5% incidence in group 1 (one of 22) and a 10% incidence in group 2 (two of 21; $P = .537$). ANOVA showed statistically significant associations of male sex and abciximab use with major bleeding complications ($P = .026$ and $P = .014$, respectively). The major bleeding complications were one case of upper gastrointestinal bleeding from a previously unknown duodenal ulcer requiring transfusion of 2 U packed red blood cells, a case of gastrointestinal bleeding requiring transfusion, and a groin hematoma requiring transfusion. A minor TNK-related bleeding complication in the form of an asymptomatic but precipitous decrease in fibrinogen level of 82% (from 359 mg/dL to 64 mg/dL) was treated with fresh frozen plasma and cryoprecipitate during continued TNK infusion. Other complications included embolus requiring aspiration embolectomy,

rapid progression to stage III ischemia in the first hour of thrombolysis requiring conversion to surgery, angioplasty with rupture of a vein graft treated with a stent, fasciotomy for compartment syndrome, surgical repair of brachial artery, anaphylactic reaction to antibiotics, and a dissection.

Fibrinogen levels averaged 396 mg/dL before thrombolysis and 335 mg/dL after thrombolysis ($P = .001$). The percentage decrease in fibrinogen level averaged 15% overall (SD, 26%), with a significantly higher percentage decrease in fibrinogen level in group 1 ($23\% \pm 29\%$) compared with group 2 ($7\% \pm 20\%$; $P = .045$). Patients with no complications had a 13% decrease in fibrinogen level, patients with complications with no relation to TNK had a 15% decrease in fibrinogen level, patients with complications with a possible relation to TNK had a -28% decrease (ie, fibrinogen increased), and patients with complications with a probable relation to TNK had a 59% decrease ($P = .001$). The percentage decrease in fibrinogen level when not ranked by likelihood of TNK as a causative factor was not associated with complications, major bleeding, or death and amputation rates. There were no major bleeding complications in the three limbs (7%) with fibrinogen levels decreasing to less than 100 mg/dL, even though one patient was classified as having a minor complication when treated prophylactically with fresh frozen plasma and cryoprecipitate for an 83% decrease in fibrinogen level from 359 mg/dL to 64 mg/dL. All three limbs with fibrinogen levels decreasing to less than 100 mg/dL were in group 1 ($P = .083$). The fibrinogen level before thrombolysis was higher in limbs in which death or amputation had occurred at 30 days and 6 months, with respective means of 598 mg/dL and 538 mg/dL compared with 381 mg/dL and 382 mg/dL, respectively, in limbs in which death or amputation did not occur ($P = .001$ and $P = .010$).

Abciximab was used in 16% of limbs ($n = 7$), 5% in group 1 (one of 22) and 29% in group 2 (six of 21; $P = .039$). Significant statistical associations were found by ANOVA between abciximab and complications, complication rank, major bleeding, and amputation at 30 days and 6 months ($P = .037$, $P = .014$, $P = .014$, $P < .001$, and

$P < .001$, respectively). Negative associations were found with technical success, but not clinical success ($P = .038$ and $P = .232$). The average infusion time for limbs treated with abciximab was 36 hours compared with 21 hours for limbs not treated ($P = .009$).

The overall amputation rates at 30 days and 6 months were 7% (three of 43) and 9% (four of 43), respectively. All amputations were below the knee. The death rates were zero at 30 days and 2% (one of 43) at 6 months. One patient died after amputation. There were no statistically significant differences between groups 1 and 2 with respect to death and amputation rates at 30 days ($P = .537$) or 6 months ($P = .290$). ANOVA showed statistically significant association of death and amputation rates with use of abciximab, preprocedural fibrinogen levels, and preprocedural ABI.

DISCUSSION

The current study shows that TNK infusion at 0.125 mg/h provides results similar to infusion at 0.25 mg/h. In turn, these results are comparable to the earlier reports in the literature with use of TNK at 0.25 mg/h and 0.5 mg/h in terms of technical success, clinical success, fibrinogen depletion, complications, and bleeding. Our technical and clinical success with TNK was consistent with these reports of TNK administered for acute limb ischemia. In these earlier reports, the technical and clinical success rates were 73%–88%, major bleeding complication rates were 1.8%–10.4%, there were no intracranial hemorrhages, and fibrinogen levels decreased 23%–41% (5–8). In group 1, we used the same infusion dose of TNK (0.25 mg/h) as in the previous reports and had nearly identical results. Our clinical success rate was 86%, major bleeding incidence was 7%, there were no intracranial hemorrhages, and the percentage decrease in fibrinogen level averaged 23%. In group 2, at half the dose, our clinical success rate was 90%, major bleeding incidence was 10%, there were no intracranial hemorrhages, and percentage decrease in fibrinogen level was 7%. It was encouraging to see that our clinical success rate remained high while the decrease in fibrinogen level was significantly less severe in group 2, suggesting that ef-

fective thrombolysis can be achieved at a dose that causes significantly less fibrinogen depletion.

Our results showed that TNK-related complications were related to TNK bolus, use of abciximab, percentage decrease in fibrinogen level, and major bleeding. The correlation with major bleeding is expected, and the correlations with abciximab and percentage decrease in fibrinogen level are discussed later. More surprising was the correlation of complications with TNK bolus but not with infusion time, TNK dose, or TNK total dose. Review of the TNK boluses showed that, even though 0–5-mg boluses were allowed, 5-mg boluses were used in only the first three cases, two of which had TNK-related complications (hematemesis and prominent decrease in fibrinogen level). Our protocol used previously reported amounts for the initial bolus (7). On further reflection, the authors thought 5 mg might be excessive in that a 24-hour infusion would use 6 mg of TNK when infused at a rate of 0.25 mg/h. A systemic lytic state might be promoted by TNK boluses of this magnitude. Based on our experience with other thrombolytic agents (ie, 250,000 to 1 million U of urokinase bolus with 2.4 million U infused over 24 hours), we began to limit our boluses to 0–3 mg TNK, most commonly 1.5 mg. Our data confirmed the concept of limiting initial boluses in that TNK boluses of 1.5 mg or less were well-tolerated, with a 22% incidence of complications (eight of 36), most of which ($n = 6$) were not TNK-related. TNK boluses of 3–5 mg had a 75% complication rate (three of four), with all three categorized as probably TNK-related.

Fibrinogen Depletion and Bleeding Complications

As noted previously, compared with tPA, TNK is a drug with a longer half-life of 22 minutes, an 80 times higher resistance to plasminogen activator inhibitor, a twofold improvement of effectiveness in arterial thrombolysis, increased fibrin specificity, and decreased fibrinogen depletion (1–3). The longer half-life allows for single bolus administration for acute myocardial infarction. In infusion for acute lower-limb ischemia, a longer half-life may have no advantage and

could possibly allow for greater levels of TNK to circulate in the bloodstream. The increased resistance to plasminogen activator inhibitor and increased effectiveness in arterial thrombolysis should make TNK more effective at the site of thrombosis. The increased fibrin specificity and decreased fibrinogen depletion may be part of a mechanism that could lead to fewer bleeding complications.

One prevalent theory suggests that bleeding with tPA and its genetic mutations reteplase and TNK is caused by fibrinogenolysis in the peripheral circulation with the accumulation of fragment X (11–13). Fragment X can clot and forms easily clots at sites of potential bleeding that can be easily lysed. If and when these clots with fragment X break down, bleeding can occur at unintended sites. For fibrinogenolysis to occur, the thrombolytic drug in the circulation needs to bind to circulating DDE (a degradation product of thrombolysis) and circulating plasminogen. Fibrinogenolysis also depletes fibrinogen (14). Thrombolytic drugs with no or low fibrin specificity (eg, urokinase and streptokinase) bind poorly to DDE, producing little fragment X. The tissue-type plasminogen activator drugs (eg, tPA, reteplase, TNK) can strongly bind DDE, but less so as the drug becomes more fibrin-specific. Stewart et al (13) showed in vitro that TNK produces less fragment X than does tPA, which produces less fragment X than reteplase, a pattern consistent with the drugs' fibrin specificity (ie, that of TNK is greater than that of tPA, which is greater than that of reteplase). On this basis, one might expect less bleeding and fibrinogen depletion when using TNK versus tPA or reteplase.

In our data, it is interesting to note that there was significantly less fibrinogen depletion at the lower infusion dose, with a 7% decrease in fibrinogen in group 2 compared with a 23% decrease in group 1. The percent decrease in fibrinogen of 15% overall in our patients and a low major bleeding complication rate of 7% may support the clinical significance of fibrin specificity and dose with respect to fibrinogenolysis in vivo. This notion was further supported by our data showing that complications rated by likelihood of TNK being the cause strongly correlated with percent drop in fibrin-

ogen, and major bleeding complications. In the clinical literature, fibrinogen depletion during thrombolysis with alteplase (15), reteplase (16,17), and TNK (7,8) has been reported to cause a drop in fibrinogen ranging from 23%–59%. In these reports, a consistent relationship between decrease in fibrinogen, drug used, and infusion dose cannot be established. Earlier reports have described an association with bleeding complications and fibrinogen depletion with use of alteplase and reteplase (18,19), whereas several other reports demonstrated no correlation (16,20,21). A recent article reporting the use of reteplase describes a 15% decrease in fibrinogen level as correlating with no bleeding complications, whereas a decrease of 72% was associated with major bleeding complications in 23% of patients (19). Our data similarly show a 15% decrease in fibrinogen levels in patients with no complications and a 59% decrease in patients with complications caused by TNK. The percentage decrease in fibrinogen appears to be a useful marker for the evaluation of the performance of thrombolytic drugs in patients with acute lower-limb ischemia and may help establish a link between thrombolytic drug, dose, fibrinogen depletion, and bleeding complications.

Abciximab

The negative association of abciximab use on technical success and its positive associations with complications in the current study are confusing. There was more abciximab use in group 2 than in group 1, but the overall outcomes of technical success, clinical success, complications, major bleeding, and SIR ischemic outcomes between the groups were not significantly different. The fact that TNK infusion times (average, 36 hours) associated with abciximab use were significantly longer than in patients who were not treated with abciximab suggests possible selection bias. The potential benefits of abciximab reported in the literature include decreased thrombolysis time, decreased embolization, improved patency, and improved thrombolysis after initial failure (19,22–24). In these studies, there were no reports of increased complications.

Intracranial Hemorrhage

There were no intracranial hemorrhages in our series. However, at our institution, we have seen an intracranial hemorrhage with TNK in a patient treated for upper-extremity embolus complicated by an asymptomatic and initially undetected right carotid artery embolus, confirming that this complication may be seen when TNK is used for thrombolytic infusion. Intracranial hemorrhage has been a major source of concern in patients undergoing thrombolysis for acute myocardial infarction, acute limb ischemia, pulmonary embolism, and deep vein thrombosis (25–29). The rate of intracranial hemorrhage during thrombolysis is reported in the range of 1%–3%. In acute myocardial infarction, the rate was reported to be less than 1% in a review of 71,073 patients (25). In a registry of 2,454 patients treated for pulmonary embolism, 3% of patients had intracranial hemorrhage (28). The incidences of intracranial hemorrhage in patients treated for acute limb ischemia and deep vein thrombosis have ranged from 0.3% to 2% (27,29,30). TNK has been shown to cause less intracranial hemorrhage than alteplase in animal studies (31), but this benefit has not been verified in humans treated for acute myocardial infarction (32). There were no intracranial hemorrhages in our series or in the other reports of TNK use in the peripheral circulation (5–8,33). Intracranial hemorrhage will continue to be a feared, expected, and hopefully rare complication of thrombolytic therapy.

The main limitations of this study are the small sample size, lack of randomization, and inconsistent use of abciximab, allowing for possible errors in analysis. Topics for future evaluation include lower TNK doses, use of glycoprotein IIb/IIIa inhibitors, alternative drug delivery catheters, and embolic protection devices.

CONCLUSION

TNK was equally effective at infusion doses of 0.25 mg/h and 0.125 mg/h, with similar success and complication rates. Initial boluses of TNK should be limited to 1.5 mg, as higher doses were associated with increased TNK-related complications. The consistent association of the use of abcix-

imab with complications and poor outcomes may be related to small sample size and selection bias; however, further evaluation of glycoprotein IIb/IIIa inhibitors is needed in acute limb ischemia. TNK may have advantages over other tPAs in terms of fibrin specificity, which may be clinically relevant in the treatment of acute lower-limb ischemia. Fibrinogen depletion was significantly decreased in the lower dose group and was significantly increased in patients with complications caused by TNK, suggesting a clinical link among TNK dose, fibrinogen depletion, and complications.

References

- Collen D, Stassen JM, Yasuda T, et al. Comparative thrombolytic properties of tissue-type plasminogen activator and of a plasminogen activator inhibitor-1-resistant glycosylation variant, in a combined arterial and venous thrombosis model in the dog. *Thromb Haemost* 1994; 72:98–104.
- Keyt BA, Paoni NF, Refino CJ, et al. A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci U S A* 1994; 91:3670–3674.
- Verstraete M. Third-generation thrombolytic drugs. *Am J Med* 2000; 109:52–58.
- Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; 354:716–722.
- Allie DE, Hebert CJ, Lirtzman MD, et al. Continuous tenecteplase infusion combined with peri/postprocedural platelet glycoprotein IIb/IIIa inhibition in peripheral arterial thrombolysis: initial safety and feasibility experience. *J Endovasc Ther* 2004; 11:427–435.
- Burkart DJ, Borsa JJ, Anthony JP, et al. Thrombolysis of occluded peripheral arteries and veins with tenecteplase: a pilot study. *J Vasc Interv Radiol* 2002; 13:1099–1102.
- Burkart DJ, Borsa JJ, Anthony JP, et al. Thrombolysis of acute peripheral arterial and venous occlusions with tenecteplase and eptifibatid: a pilot study. *J Vasc Interv Radiol* 2003; 14:729–733.
- Razavi MK, Wong H, Kee ST, et al. Initial clinical results of tenecteplase (TNK) in catheter-directed thrombolytic therapy. *J Endovasc Ther* 2002; 9:593–598.
- Rutherford R, Baker J, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vascular Surgery* 1997; 26:517–538.

10. 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.
11. 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.
12. Owen J, Friedman KD, Grossman BA, et al. Quantitation of fragment X formation during thrombolytic therapy with streptokinase and tissue plasminogen activator. *J Clin Invest* 1987; 79:1642-1647.
13. Stewart RJ, Fredenburgh JC, Leslie BA, et al. 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.
14. Weitz JI, Leslie B, Ginsberg J. Soluble fibrin degradation products potentiate tissue plasminogen activator-induced fibrinogen proteolysis. *J Clin Invest* 1991; 87:1082-1090.
15. 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.
16. Davidian MM, Powell A, Benenati JF, et al. Initial results of reteplase in the treatment of acute lower extremity arterial occlusions. *J Vasc Interv Radiol* 2000; 11:289-294.
17. Drescher P, McGuckin J, Rilling WS, et al. Catheter-directed thrombolytic therapy in peripheral artery occlusions: combining reteplase and abciximab. *AJR Am J Roentgenol* 2003; 180:1385-1391.
18. 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.
19. Hull JE, Hull MK, Urso JA. Reteplase with or without abciximab for peripheral arterial occlusions: efficacy and adverse events. *J Vasc Interv Radiol* 2004; 15:557-564.
20. 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.
21. 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.
22. 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.
23. Nakada MT, Montgomery MO, Nedelman MA, et al. Clot lysis in a primate model of peripheral arterial occlusive disease with use of systemic or intraarterial reteplase: addition of abciximab results in improved vessel reperfusion. *J Vasc Interv Radiol* 2004; 15:169-176.
24. Ouriel K, Castaneda F, McNamara T, et al. Reteplase monotherapy and reteplase/abciximab combination therapy in peripheral arterial occlusive disease: results from the RELAX trial. *J Vasc Interv Radiol* 2004; 15:229-238.
25. Gurwitz JH, Gore JM, Goldberg RJ, et al. Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. Participants in the National Registry of Myocardial Infarction 2. *Ann Intern Med* 1998; 129:597-604.
26. 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.
27. Costantini V, Lenti M. Treatment of acute occlusion of peripheral arteries. *Thromb Res* 2002; 106:V285-V294.
28. Goldhaber SZ. Modern treatment of pulmonary embolism. *Eur Respir J* 2002; 35(suppl):22s-27s.
29. Mewissen MW, Seabrook GR, Meissner MH, et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology* 1999; 211:39-49.
30. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med* 1998; 338:1105-1111.
31. Smalling RW. Molecular biology of plasminogen activators: what are the clinical implications of drug design? *Am J Cardiol* 1996; 78:2-7.
32. Dunn CJ, Goa KL. Tenecteplase: a review of its pharmacology and therapeutic efficacy in patients with acute myocardial infarction. *Am J Cardiovasc Drugs* 2001; 1:51-66.
33. Allie DE, Hebert CJ, Lirtzman MD, et al. Novel simultaneous combination chemical thrombolysis/rheolytic thrombectomy therapy for acute critical limb ischemia: the power-pulse spray technique. *Cathet Cardiovasc Interv* 2004; 63:512-522.