The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions

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Purpose: **The purpose of this study was to compare the efficacy, complications, and costs associated with low-dose (≤2 mg/h) alteplase (tissue plasminogen activator [t-PA]) versus urokinase for the catheter-directed treatment of acute peripheral arterial occlusive disease (PAO) and deep vein thrombosis (DVT).**
Materials and methods: **A retrospective review was performed during sequential time periods on two groups with involved extremities treated with either t-PA with subtherapeutic heparin (TPA group) or urokinase with full heparin (UK group) at a single center. Treatment group characteristics, success rates, complications, dosages, infusion time, and costs were compared.**
Results: **Eighty-nine patients with 93 involved limbs underwent treatment (54 with DVT, 39 with PAO). The treatment groups were statistically identical (TPA: 45 limbs; 24 with DVT, 53.3%; 21 with PAO, 46.7%; UK: 48 limbs; 30 with DVT, 62.5%; 18 with PAO, 37.5%). The overall average hourly infused dose, total dose, infusion time, success rates, and cost of thrombolytic agent were as follows (± standard deviation): TPA, 0.86 ± 0.50 mg/h, 21.2 ± 15.1 mg, 24.6 ± 11.2 hours, 89.4%, $466 ± $331; and UK, 13.5 ± 5.6 (10^4) U/h, 4.485 ± 2.394 million U, 33.3 ± 13.3 hours, 85.7%, $6871 ± $3667, respectively. Major and minor complication rates were: TPA, 2.2% and 8.9%; and UK, 2.1% and 10.4%, respectively. No statistical differences in success rates or complications were observed; however, t-PA was significantly ($P < .05$) less expensive and faster than urokinase.**
Conclusion: **Low-dose t-PA combined with subtherapeutic heparin is equally efficacious and safe compared with urokinase. Infusions with t-PA were significantly shorter and less expensive than those with urokinase. (J Vasc Surg 2003;37:512-7.)**

Although surgical intervention has been the historic standard of care for treatment of acute peripheral arterial occlusive (PAO) disease, catheter-directed thrombolysis has been useful in the rapid removal of large clot burdens, the unmasking of underlying lesions, and the simplification of subsequent percutaneous or surgical treatments.[1-3] Similarly, thrombolysis has emerged as an alternative to anticoagulation therapy for management of extensive symptomatic deep vein thrombosis (DVT) of the upper and lower extremities.[4,5] Urokinase (Abbokinase, Abbott Laboratories, Chicago, Ill), a second-generation plasminogen activator, has been the dominant thrombolytic agent of choice for catheter-directed therapy for the past 20 years on the basis of its consistency and predictability. However, the US Food and Drug Administration suspended the distribution of Abbokinase in the United States in late 1998 because of the theoretic and remote risk of viral disease transmission arising from harvested human neonatal kidney cells.[6] The unavailability of urokinase has forced practitioners to search for suitable alternative agents.

Alteplase (tissue plasminogen activator [t-PA]; Activase, Genentech, Inc, San Francisco, Calif), a recombinantly derived analog of human t-PA, has become the predominant replacement in the United States for catheter-directed therapy, thrombolysis of occluded dialysis grafts, and management of thrombosed central venous access devices. Because of the need for thrombolysis protocols with recombinant agents, an Advisory Panel to the Society of Cardiovascular and Interventional Radiology published guidelines recommending use of "low-dose" (≤2 mg/h) alteplase and subtherapeutic heparin for catheter-directed treatment of PAO and DVT on the basis of the clinical experience of the Panel members.[7] Recently, Ouriel et al[8] reported significantly higher bleeding rates when compar-

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ing alteplase (22.2%) with urokinase (12.4%), but the doses of alteplase (0.05 to 0.1 mg/kg/h) and anticoagulation regimens used significantly exceeded the safety guidelines recommended by the Advisory Panel. Unfortunately, no peer-reviewed data exist comparing "low-dose" alteplase infusions with established urokinase protocols, and many questions remain in regards to the risks associated with alteplase. The purpose of this study was to report the safety, efficacy, and pharmacoeconomics of alteplase compared with urokinase from a single center.

MATERIALS AND METHODS

Inclusion criteria for this retrospective analysis were acute (<14 days) limb ischemia (International Society for Cardiovascular Surgery/Society for Vascular Surgery classification I-3 or II) or acute (≤30 days) symptomatic DVT of the limb in patients who underwent catheter-directed therapy with urokinase or alteplase.[9] Informed consent was obtained for all patients before therapy. Before December 1998, urokinase was the exclusive thrombolytic agent used at our institution. Alteplase was used from December 1998 to June 2000. However, during the transition period, four patients (eight extremities) received urokinase during the initial therapeutic encounter and alteplase on a subsequent separate encounter. Urokinase data were collected from consecutive patients from October 1997 to February 1999 to ensure that the most recent protocols were being used. Alteplase data were collected in consecutive patients from December 1998 through June 2000.

Interventional procedures were performed in a dedicated angiography suite by full-time, subspecialty board-certified vascular interventional radiologists, each with a minimum experience of 100 cases of catheter-directed therapy. Vascular access was obtained with a 21-G micropuncture set (Cook, Inc, Bloomington, Ind) and single wall arterial entry, whenever possible. For patients with extensive vascular disease and pulses that were difficult to palpate, ultrasound scan–guided assistance was used (Site Rite, Dymax/Bard Vascular Access, Salt Lake City, Utah). An intrathrombic multislit infusion system (5F Unifuse, AngioDynamics, Glen Falls, NY) was placed for continuous overnight infusion of either drug with endovascular techniques described previously.[4,10] No bolus, prelacing, pulse-spray, or mechanical thrombectomy was performed. All patients were observed overnight in a coronary step-down unit where the staff was specifically trained to monitor for bleeding complications and follow coagulation parameters. The patients returned to the angiography suite the next morning. The protocol for angiographic follow-up was the same for both the alteplase and urokinase groups.

The initial hourly infused dose of either urokinase or t-PA was decided by the interventional radiologist in consideration of the clinical background and general condition of the patient. For all patients, the fibrinogen values were monitored at 6-hour to 8-hour intervals and the thrombolytic doses titrated to maintain the fibrinogen above 100 mg/dL; however, the individual fibrinogen data were not retrospectively collected for analysis. Termination of the lytic infusion was based on the results of the follow-up angiogram. If the angiogram showed complete lysis, the infusion was terminated; for partial lysis, the infusion was continued for another 6 to 24 hours after repositioning of the catheter system; and if no lysis was seen, the procedure was either terminated and considered a technical failure or given another 6 to 24 hours of lytic therapy at the discretion of the interventional radiologist.

For the urokinase treatment group, 500,000 U of urokinase (Abbokinase) were diluted in 500 mL of normal saline solution and infused at approximately 120,000 IU/h (range, 50,000 to 240,000 U/h, 120 to 240 mL/h). Patients underwent anticoagulation therapy with unfractionated heparin to maintain the partial thromboplastin time at 1.5 to two times the baseline. Heparin was administered either through a peripheral intravenous line or through the outer sheath. For the t-PA treatment group, t-PA (Activase) was kept reconstituted (1 mg/mL) and frozen (−20° C) in 2-mg sterile glass vials.[11] Before the initiation of thrombolytic therapy, t-PA vials were thawed and immediately diluted in normal saline solution to a final concentration of usually 0.02 mg/mL for infusion (range, 0.01 to 0.02 mg/mL, 25 to 50 mL/h; Genentech, Inc, unpublished data). Dosing of alteplase was based on the recommendations of the Advisory Panel to the Society for Cardiovascular and Interventional Radiology on Thrombolytic Therapy.[7] Alteplase was infused with a non–weight-based regimen at the typical rate of 0.5 mg/h for PAO and 1.0 mg/h for DVT (range, 0.25 to 2.0 mg/h). Subtherapeutic heparin was administered through the outer sheath to maintain the partial thromboplastin time at less than 1.5 times the baseline.

Outcome variables. Outcome variables included initial and total drug doses, infusion time, success rates, complications, and estimated drug costs. Thrombolysis was defined as complete (<5% residual clot), partial, or failure (no angiographic evidence of lysis). Successful thrombolysis was defined as complete or partial lysis with: 1, PAO, improvement of the International Society for Cardiovascular Surgery/Society for Vascular Surgery scale by one or more classifications; or 2, DVT, resolution of the acute pain and edema of the extremity after intervention. Major complications were defined as death, intracranial hemorrhage, bleeding requiring transfusion or surgery, or increase in length of hospital stay. Minor complications were defined as adverse events requiring only conservative therapy, such as small access site hematomas. Analysis of estimated drug costs were based on the list price for urokinase in 1998 ($383/250,000 IU vial) or alteplase in 1999, which had been reconstituted, aliquotted in 2-mg vials, and frozen ($22/mg). The treatment group characteristics, infusion time, success rates, complications, and estimated drug costs were compared with the Student *t* test for continuous data and χ^2 analysis for dichotomous data. The predictors of thrombolytic complications associated with each drug were analyzed with multivariable logistic regression analysis. A *P* value of less than .05 was considered to be statistically significant.

Table I. Baseline characteristics of 96 treated extremities in 89 patients

	t-PA	*UK*	P *value*
Gender			
Male	22 (48.9%)	22 (45.8%)	.77
Female	23 (51.1%)	26 (54.2%)	.77
Age (years ± standard deviation)			
Overall	52.2 ± 19.6	53.6 ± 19.2	.72
DVT	43.5 ± 17.6	46.0 ± 17.5	.60
PAO	62.2 ± 17.2	66.4 ± 15.0	.43
Disease/location			
DVT (n = 54)	24 (44.4%)	30 (55.6%)	.37
Upper extremity (n = 22)	12 (54.5%)	10 (45.5%)	.22
Lower extremity (n = 32)	12 (37.5%)	20 (62.5%)	.22
PAO (n = 39)	21 (53.8%)	18 (46.2%)	.37
Native artery (n = 23)	10 (43.5%)	13 (56.5%)	.12
Bypass graft (n = 16)	11 (68.8%)	5 (31.3%)	.12

RESULTS

Patient baseline characteristics. Eighty-nine patients (43 men, 46 women; mean [± standard deviation] age, 52.4 ± 19.3 years) with 93 involved extremities underwent treatment with catheter-directed thrombolysis. The gender, age, disease type, and anatomic location were not statistically different for extremities treated with t-PA (TPA group) or urokinase (UK group; Table I).

Details of thrombolysis. The infusion times overall (PAO and DVT) and for each disease group (PAO or DVT) were significantly shorter in the TPA group compared with the UK group ($P < .05$; Table II). Similarly, the drug costs overall and for each disease group were significantly less expensive in the TPA group compared with the UK group ($P < .0001$).

The average overall hourly infusion dose, total dose, infusion time, and estimated drug costs (respectively) for t-PA versus urokinase were: TPA, 0.86 ± 0.50 mg/h, 21.2 ± 15.1 mg, 24.6 ± 11.0 hours, and $466 ± $331; and UK, 13.5 ± 5.6 (10^4) U/h, 4.485 ± 2.394 (10^6) U, 33.3 ± 13.3 hours, and $6871 ± $3667.

Success and complication rates. Results of thrombolysis were not statistically different for each treatment group (Table III). The percentages of thrombolytic success (complete and partial) overall and for each disease group, respectively, were: TPA, 88.9%, 87.5% for DVT, and 90.5% for PAO; UK, 85.4%, 83.4% for DVT, and 88.9% for PAO.

No statistical differences were seen in major or minor bleeding between the two groups (Table III). Both groups had one major complication. One patient receiving t-PA (2.2%) had spontaneous lower gastrointestinal bleeding (melena) and underwent conservative treatment with 2 units of packed red blood cells. One patient receiving urokinase (2.1%) had a large access site hematoma and underwent treatment with 2 units of packed red blood cells. There were no deaths, intracranial hemorrhage, need for intensive care unit monitoring, or surgical interventions in either group. Four patients treated with t-PA (8.9%) and five with urokinase (10.4%) had minor bleeding events. All nine patients had access site–related hematomas; however, no intensive care unit monitoring, operative repair, or blood transfusions were required. There were no observed signs of systemic fibrinolysis (eg, gingival bleeding, bleeding from the oral mucosa, epistaxis, or subcutaneous ecchymoses [purpura thrombolyticus]) in either treatment group.[12]

Multivariable logistic regression analysis of complications. Univariate and multivariate analysis of variables affecting complications showed no statistically significant predictors of adverse outcomes (Table IV). Age, gender, disease type, location, hourly infusion rate, total drug dose, and total infusion time were nonpredictive in this study.

DISCUSSION

For the past two decades, urokinase has been the dominant and virtually exclusive agent used for peripheral thrombolytic therapy in the United States. Dotter, Rosch, and Seaman[13] first showed that intrathrombic delivery of streptokinase, a first-generation agent, was far more efficient in lysing arterial thrombus than systemic intravenous infusion. Subsequent studies with the second generation agent, urokinase, with improved fibrin specificity, showed a more efficacious and improved safety profile compared with streptokinase.[14,15] Urokinase rapidly gained favor because of its consistency, predictability, and lack of antigenic complications. Despite the availability of recombinant t-PA, few investigators explored the peripheral use of t-PA in the United States.[16,17] Urokinase remained the exclusive agent because the general prevailing opinion was that t-PA was vastly more expensive and far more prone to hemorrhagic complications compared with urokinase ($1100 vial Activase compared with $383 vial of Abbokinase) despite the lack of formal large-scale comparative clinical trials. In 1999, the US Food and Drug Administration abruptly suspended the distribution of Abbokinase because of possible viral contamination of bulk tissue before processing.[18] Abbokinase is derived from kidney cell tissue culture from neonatal renal tissue procured in Colombia, South America. The impact of the shortage was felt immediately; most American and Canadian practitioners had no prior experience with t-PA as an alternative, and optimal doses were not understood. Early studies with t-PA reported excessive major bleeding complications (22% to 33%).[8,19] Because of the need for safe practice guidelines, the Society of Cardiovascular and Interventional Radiology assembled a multidisciplinary Advisory Panel to formulate recommendations on alternatives to urokinase.[7] The Panel recommended that t-PA should be dosed 2 mg/h or less (median range, 0.5 to 1.0 mg/h) with low-dose heparin. The purpose of this study was to compare the safety, efficacy, and costs of t-PA infusions with the Advisory Panel guidelines compared with our prior established experience with urokinase.

With the Advisory Panel guidelines, alteplase was equally efficacious as urokinase for acute arterial thrombosis but required shorter infusion times ($P < .0009$). The

Table II. Details of thrombolytic infusion

	t-PA	*UK*	P *value*
Hourly infused dose (± standard deviation)			
Overall	0.86 ± 0.50 mg/h	13.5 ± 5.6 10^4 U/h	
DVT	0.96 ± 0.54 mg/h	15.0 ± 6.3 10^4 U/h	
PAO	0.76 ± 0.46 mg/h	11.0 ± 2.8 10^4 U/h	
Total drug dose (± standard deviation)			
Overall	21.2 ± 15.1 mg	4.485 ± 2.394 million U	
DVT	23.2 ± 15.1 mg	4.836 ± 2.662 million U	
PAO	19.0 ± 15.2 mg	3.938 ± 1.849 million U	
Infusion time (h ± standard deviation)			
Overall	24.6 ± 11.0	33.3 ± 13.3	.0009
DVT	24.1 ± 10.6	33.4 ± 14.2	.0110
PAO	25.1 ± 11.6	32.3 ± 12.0	.0390
Drug costs ($)			
Overall	466 ± 331	6871 ± 3667	<.0001
DVT	511 ± 331	7408 ± 4078	<.0001
PAO	418 ± 334	6032 ± 2833	<.0001

overall complete/partial lysis rate (90.5% t-PA, 83.3% urokinase; $P = .7$) was consistent with results of other studies comparing t-PA with urokinase for PAO.[20,21] Graor, Olin, and Bacharach[20] reported the results of a randomized prospective pilot trial comparing t-PA (0.05 mg/kg/h × 24 hours) versus urokinase (240,000 U/h) for treatment of acute limb ischemia in 45 patients and reported a success rate of 91% with t-PA and 86% with urokinase with a faster time to reperfusion with t-PA. The STILE (Surgery versus Thrombolysis for Ischemia of the Lower Extremity) study was a formal large-scale comparative clinical trial that compared surgical revascularization versus thrombolysis for the management of acute and chronic limb ischemia. The thrombolysis arm was further randomized to urokinase (n = 112; 250,000 U bolus, then 240,000 U/h × 4 hours, then 120,000 U/h × 36 hours) or t-PA (n = 137; 0.1 mg/kg/hr × 12 hours, then decreased to 0.05 mg/kg/h × 12 hours during the trial). No statistical differences were seen in outcome or complications between the t-PA or urokinase groups. Our results indicate that a high rate of efficacy can be achieved at far lower doses (0.76 ± 0.5 mg t-PA) compared with prior reports that used weight-adjusted doses equivalent to 4 to 8 mg/h in an 80-kg patient.[16,20] The overall t-PA doses in our study averaged 19.0 mg/patient, which is nearly 2.5-fold to five-fold lower a dose compared with the Graor, Olin, and Bacharach[20] or STILE trials.[21]

The results of venous thrombolysis with t-PA (87.5% complete/partial lysis) were consistent with previously reported small series[22-25] and appeared equally efficacious and safe compared with our prior experience with urokinase,[5] except for a requirement for significantly shorter infusion times. The only comparative study evaluating t-PA versus urokinase for DVT was a randomized prospective trial involving 69 patients.[26] Patients with acute DVT were randomized to one of three treatment groups: heparin alone, catheter-directed t-PA (5 mg/h × 4 hours), or urokinase (100,000 U/h × 7 days). The urokinase group showed 50% lysis compared with 27% for the t-PA group. At 1-year follow-up, the urokinase group showed fewer postthrombotic complications compared with the t-PA or heparin group, but arguably, the outcomes may be more a manifestation of thrombolytic technique than inherent differences in the molecules.

Table III. Outcomes of thrombolytic therapy

	t-PA	*UK*	P *value*
Thrombolytic success			
Overall (DVT and PAO)			
Complete	27 (60.0%)	26 (54.2%)	.57
Partial	13 (28.9%)	15 (31.2%)	.80
None	5 (11.1%)	7 (14.6%)	.62
Complete/partial	40 (88.9%)	41 (85.4%)	.40
DVT			
Complete	14 (58.3%)	14 (46.7%)	.39
Partial	7 (29.2%)	11 (36.7%)	.56
None	3 (12.5%)	5 (16.6%)	.67
Complete/partial	21 (87.5%)	25 (83.3%)	.69
PAO			
Complete	13 (61.9%)	12 (66.7%)	.76
Partial	6 (28.6%)	4 (22.2%)	.65
None	2 (9.5%)	2 (11.1%)	.87
Complete/partial	19 (90.5%)	16 (88.9%)	.90
Complications			
Major	1 (2.2%)	1 (2.1%)	.96
Minor:overall	4 (8.9%)	5 (10.4%)	.80
DVT	2 (4.4%)	2 (4.2%)	.82
PAO	2 (4.4%)	3 (6.3%)	.51

Major and minor adverse bleeding complications were equivalent in both treatment groups. With low-dose alteplase as an alternative to urokinase, we could not support the earlier observations that t-PA has a higher rate of adverse bleeding compared with urokinase. The discrepancy between our data and prior reports may be attributable to: 1, lower hourly infused doses of t-PA; 2, lower overall doses; 3, implementation of low-dose heparin regimens; and 4, dedicated full-time interventional radiologists

Table IV. Analysis of variables affecting complications of treated extremities

	Complication		P *value*	
Variable	*Yes*	*No*	*Univariate*	*Multivariate*
TPA				
Age (y; ± SD)	53.5 ± 19.0	42.2 ± 23.7	.23	–
Gender				
Male	4	23	.14	–
Female	1	23	.14	–
Disease				
DVT	2	22	.53	–
PAO	3	18	.53	–
Infusion				
Rate (mg/h; ±SD)	1.13 ± 0.75	0.83 ± 0.48	–	.78
Total dose (mg; ±SD)	26.8 ± 19.8	20.6 ± 14.7	–	.54
Infusion time (h; ±SD)	22.4 ± 3.6	24.9 ± 11.6	–	.93
UK				
Age (y; ±SD)	51.2 ± 14.9	54.0 ± 19.9	.74	–
Gender				
Male	3	19	.83	–
Female	3	23	.83	–
Disease				
DVT	2	28	.11	–
PAO	4	14	.11	–
Infusion				
Rate (10^4 U/h; ±SD)	12.2 ± 1.6	13.7 ± 6.0	–	.84
Total dose (million U; ±SD)	4.83 ± 1.72	4.42 ± 2.82	–	.51
Infusion time (h; ±SD)	38.3 ± 10.6	32.6 ± 13.6	–	.70

SD, Standard deviation.

with extensive experience in catheter-directed therapy.[8,19] One of these studies[19] did included a full-time interventional radiologist, although it was early in the t-PA experience. In a metaanalysis of 12 studies involving 1291 patients undergoing catheter-directed therapy with t-PA, the overall incidence rate of major adverse bleeding was 5.1% (range, 0 to 17%) with t-PA,[27] similar to the reported experience with urokinase.[2,21,28,29] A recent Cleveland Clinic registry of 653 consecutive patients treated with urokinase or t-PA showed significantly higher major bleeding (22.2%) and intracranial hemorrhage (2.8%) rates in the t-PA treatment group.[8] However, analysis of the t-PA treatment group showed significantly larger hourly (0.05 to 0.1 mg/kg/h × 24 hours, full heparin) and overall doses than our series—doses that were nearly 500% to 900% higher. No intracranial bleeding was experienced in our experience in either treatment group. Minor adverse bleeding rates of t-PA and urokinase were 8.9% and 10.4%, respectively.

Variables associated with adverse bleeding remain controversial. Thomas and Gaines[30] investigated factors associated with an increased risk of complications during thrombolysis with univariate and multivariate analysis of 798 patients in a British thrombolytic registry database, most of whom were treated with t-PA in doses ranging from 0.5 to 5 mg/h. Case selection appeared to be the most important factor influencing the occurrence of complications, and radiologic technique, such as agent used, sheath size, length of lysis, dose of lysis, use of heparin or adjunctive procedures, had no relationship to the rate of complications. Univariate and multivariate analysis of our patients did not reveal positive predictors of adverse events, presumably because of the small data sets for both treatment groups.

Pharmacoeconomic analysis showed significant cost savings with t-PA compared with urokinase. T-PA was nearly 15 times less expensive than urokinase overall. For every 100 patients treated, the use of t-PA would save our institution approximately $600,000. Even considering the costs associated with aliquotting and freezing t-PA into 2-mg vials, the cost savings remain substantial.

The interpretations of this study are limited by it being a small, retrospective, nonrandomized analysis from a single center. Moreover, it is possible that because this was a sequential comparison between urokinase and t-PA, our results favor t-PA as interventional techniques have improved with time. However, favorable outcomes of this preliminary study suggest that low-dose t-PA, when following the Advisory Panel guidelines, is equally efficacious and safe compared with traditional urokinase regimens, with a shorter duration of thrombolysis and significant cost savings overall. Confirmation of these findings is warranted on a large, randomized, prospective, multicenter basis.

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