Safety and efficacy of limited-dose tissue plasminogen activator in acute vascular occlusion

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***Objective*: The purposes of this study were to evaluate the safety and efficacy of limited-dose tissue plasminogen activator (t-PA) in patients with acute vascular occlusion and to compare these results with those obtained in equivalent patients receiving urokinase.**

***Methods:* We compared the results of 60 patients receiving catheter-directed urokinase from November 1997 to November 1998 (240,000 units/h × 4 h, 120,000 units/h thereafter for a maximum of 48 h) with those of 45 patients receiving catheter-directed t-PA from November 1998 to August 2000 (2 mg/h, total dose ≤100 mg) for acute arterial occlusion (AAO) and acute venous occlusion (AVO). Interventional approaches such as cross-catheter and coaxial techniques were used to reduce the dose of lytic agent needed to achieve pre–lysis-treatment goals (eg, complete lysis of all thrombus/unmasking graft stenosis or establishing outflow target). Statistical analysis was performed using Student *t* test and Fisher exact test.**

***Results:* The urokinase and t-PA groups were comparable with regard to age, comorbidities (coronary artery disease, hypertension, diabetes, renal insufficiency, smoking), duration of ischemic or occlusive symptoms, location of occlusive process, pretreatment with warfarin, and thrombotic versus embolic and native versus graft occlusion in patients with AAO. In patients with AAO and in those with AVO, t-PA was equivalent to or better than urokinase with regard to percent of clot lysis, incidence of major bleeding complications, limb salvage, and mortality. Achievement of pretreatment goals (arterial patients only) was 50% for urokinase patients and 76% for t-PA patients ($P = .02$). Analysis of success in individual pretreatment-goal achievement showed urokinase and t-PA to be equivalent in unmasking stenoses (85% and 84%, respectively; P = NS), whereas t-PA was superior to urokinase in the more critical task of establishing run-off (39% versus 81% for urokinase and t-PA, respectively; $P = .001$). Additional interventions, either endovascular or surgical, were required in 60% and 51% (P = NS) of patients receiving urokinase and t-PA, respectively, for AAO, and in 54% and 62% (P = NS) of patients receiving urokinase and t-PA, respectively, for AVO.**

***Conclusions:* Limited-dose t-PA is a safe and effective therapy for AAO and AVO when administered by experienced teams using innovative but well-established interventional techniques. (J Vasc Surg 2001;34:854-9.)**

Urokinase has been the agent of choice in the treatment of acute arterial and venous occlusions in most medical centers for the past decade.[1-3] The removal of urokinase from the market in November 1998 has forced interventional radiologists and vascular surgeons to use alternative thrombolytic agents in the treatment of acute peripheral vascular thrombosis. Previous experience with tissue plasminogen activator (t-PA) has resulted in the perception that this agent may be as effective as urokinase but is associated with a higher rate of major bleeding complications, especially the most feared complication of intracranial hemorrhage. Given the current unavailability of urokinase, we sought to determine whether these perceptions were justified or whether there were other factors that affected the results of earlier studies in which t-PA was used to treat vascular occlusions. Some earlier studies involving t-PA used doses of 5 mg/h and higher, compared with the present study in which the highest dose employed was 2 mg/h, with a maximum dose of 100 mg total. In addition, there have been significant advances made in the technical aspects of administration of lytic agents, resulting in improved outcomes and shorter infusion times. This study was undertaken to determine whether urokinase and t-PA may in fact be equivalent with regard to safety and efficacy if used in the setting of current interventional techniques and lower dosing.

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PATIENTS AND METHODS

After urokinase became unavailable in November 1998, patients presenting with acute arterial occlusion (AAO) or acute venous occlusion (AVO) at our institution were treated with t-PA. This group of patients, treated between November 1998 and August 2000, was compared in retrospective fashion with the cohort of patients treated with urokinase for the 12-month period (November 1997 to November 1998) immediately preceding. Between November 1997 and August 2000, no substantive changes occurred with regard to the technique

Table Ia. Patient demographics for arterial occlusions

Agent	*Age (y)*	*Male (%)*	*CAD (%)*	*Hypertension (%)*	*Diabetes (%)*	*Renal failure (%)*	*Smoking (%)*	*Warfarin (%)*
Urokinase (n = 6)	63.9	19 (53)	17 (47)	25 (69)	22 (61)	5 (14)	23 (64)	12 (33)
t-PA (n = 37)	63.7	15 (41)	16 (43)	26 (70)	20 (54)	5 (14)	20 (54)	11 (30)
P value	NS	NS	NS	NS	NS	NS	NS	NS

CAD, Coronary artery disease.

Table Ib. Patient demographics for venous occlusions

Agent	*Age (y)*	*Male (%)*	*CAD (%)*	*Hypertension (%)*	*Diabetes (%)*	*Renal failure (%)*	*Smoking (%)*	*Warfarin (%)*
Urokinase (n = 23)	40.1	12 (52)	4 (17	4 (17)	6 (26)	0	4 (17)	7 (30)
t-PA (n = 8)	44.8	4 (50)	1 (12)	2 (25)	1 (12)	0	2 (25)	2 (25)
P value	NS	NS	NS	NS	NS		NS	NS

CAD, Coronary artery disease.

of administration of thrombolytic agent. Results in patients treated for AAO and AVO were analyzed separately.

Acute arterial occlusions

Retrospective chart review was conducted on 36 patients receiving urokinase for AAO and 37 patients receiving t-PA for AAO at Strong Memorial Hospital between November 1997 and August 2000.

The groups were equivalent with regard to age, sex, comorbidities, pretreatment with warfarin, duration of occlusion, nature and severity of ischemic symptoms, location of occlusion, presence of native versus graft occlusion, presence of thrombotic versus embolic occlusion (Tables Ia, IIa). In the urokinase group, 17 of the 22 grafts were autogenous and 5 were prosthetic, whereas in the t-PA group, 20 of the 27 grafts were autogenous and 7 were prosthetic. In the urokinase group, there were 14 femoropopliteal grafts, 4 femorotibial grafts, 2 inflow conduits, and 2 patients with both inflow and outflow conduits. In the t-PA group, there were 15 femoropopliteal grafts, 7 femorotibial grafts, 3 inflow conduits, and 2 patients with both inflow and outflow conduits.

Indications for thrombolysis. Patients with acute (14 days or less) Society for Vascular Surgery/International Society for Cardiovascular Surgery class IIa or IIb ischemia[4] caused by thrombotic or embolic occlusion of a native artery or bypass graft were considered eligible for thrombolysis.

Exclusion criteria. Exclusion criteria included any history of major hemorrhage involving the brain or gastrointestinal tract, pregnancy, age of less than 18 years, bleeding diathesis (excluding pharmacologic), recent (<14 days) surgery or trauma, inability to traverse the clot with a guidewire, and embolic occlusion of the common femoral artery in the absence of peripheral vascular disease.

Techniques of administration. Diagnostic arteriography was performed via the contralateral extremity, or, if this was not possible, from the axillary approach. Lytic agent was administered directly into the thrombus in all instances, with use of coaxial catheter systems and cross-catheter techniques when necessary. Pulse-spray catheter techniques were not used routinely.

Dosing and use of heparin. Urokinase was administered at 240,000 units/h for the first 4 hours and reduced to 120,000 units/h thereafter, for a maximum of 48 hours. The mean total dose of urokinase was 4,676,167 units. t-PA was administered at 2 mg/h for a maximum of 100 mg with no initial bolus and a mean total dose of 51.2 mg. Low-dose intravenous heparin (500 units/h) was used to prevent pericatheter thrombosis in all patients.

Fibrinogen levels were not routinely monitored, because it is not the policy at our institution to alter therapy based on fibrinogen values alone. This is based on data from previous studies demonstrating that fibrinogen levels correlate poorly with clinical risk of bleeding.[3,5,6] The decision to discontinue thrombolytic therapy was made on the basis of clinically significant bleeding only.

Efficacy endpoints. The efficacy of the lytic agent was assessed by determining the percentage of clot lysis achieved in each patient (percent lysis was estimated by a single, blinded observer comparing prelysis and postlysis angiograms and multiplying the length of occlusion by the vessel diameter), the amount of time required to achieve complete lysis, 30-day limb salvage and mortality, need for additional interventions after administration of lytic agent, and achievement of pretreatment goals. Pretreatment goals (either complete lysis of all thrombus/unmasking of underlying stenosis or establishing run-off) were identified retrospectively in blinded fashion.

Safety endpoints. The safety of each agent was determined by establishing the relative incidence of major hemorrhage (bleeding requiring transfusion or operative intervention or that was considered to be life-threatening), minor hemorrhage (bleeding not meeting the aforementioned criteria, such as local hematoma formation, or modest bleeding at catheter insertion or remote sites), intracranial hemorrhage, and allergic reaction.

Table IIa. Occlusive process in arterial patients

Agent	*Sx duration (h)*	*Infrainguinal (%)*	*Suprainguinal (%)*	*Thrombosis (%)*	*Embolus (%)*	*Native (%)*	*Graft (%)*
Urokinase (n = 36)	4.9	28 (78)	8 (22)	30 (83)	6 (17)	14 (39)	2 (61)
t-PA (n = 37)	2.9	28 (76)	9 (24)	33 (89)	4 (11)	10 (27)	27 (73)
P value	NS	NS	NS	NS	NS	NS	NS

Sx, Symptom.

Table IIb. Occlusive process in venous patients

Agent	*Upper-extremity Sx duration (d)*	*Lower-extremity thrombosis (%)*	*Predisposing thrombosis (%)*	*factors (%)*
Urokinase (n = 23)	3.5	6 (26)	17 (74)	18 (78)
t-PA (n = 8)	3.9	2 (25)	6 (75)	6 (75)
P value	NS	NS	NS	NS

Sx, Symptom.

Acute venous occlusions

Charts from 23 patients receiving urokinase and eight receiving t-PA were reviewed from the same time period and institution as noted above. The two groups were equivalent with regard to age, sex, comorbidities, pretreatment with warfarin, duration of occlusion, nature and severity of occlusive symptoms, and location of occlusion (Tables Ib, IIb).

Indications for thrombolysis. Patients with acute (14 days of symptoms or less) venous thrombosis (excluding catheters and arteriovenous fistulae) were considered eligible for thrombolysis.

Exclusion criteria. The same criteria were applied as in patients with AAO, with the exception of common femoral emboli.

Dosing and use of heparin. Dosing and use of heparin, techniques of administration of lytic agent, and monitoring of fibrinogen levels were comparable with those used for patients with AAO. The mean total dose of urokinase was 4,618,542 units, and the mean total dose of t-PA was 81.5 mg.

Efficacy endpoints. The efficacy of the lytic agent was assessed by determining the percentage of clot lysis achieved in each patient (using analysis of prelysis and postlysis venograms), the amount of time required to achieve complete lysis, and the need for additional interventions after administration.

Safety endpoints. The safety of each agent was determined by establishing the relative incidence of major and minor hemorrhage and other criteria outlined previously. Statistical analysis was performed using the Student two-tailed *t* test for continuous variables and the Fisher exact test for proportions in both groups of patients.

RESULTS

Acute arterial occlusion. There were no significant differences between the two groups with regard to 30-day mortality, major and minor hemorrhage, need for additional intervention, length of stay, and achievement of individual pretreatment goals (Table III). One major bleeding event (3%) occurred in each of the groups; in both cases this was bleeding from a catheter insertion site, and both patients required operative intervention to correct the problem. Minor bleeding events occurred in five of the patients in the t-PA group (14%) and four of the patients in the urokinase group (11%). Distal emboli were noted in eight patients receiving urokinase and four patients receiving t-PA.

Four patients died within 30 days of undergoing thrombolysis; in the t-PA group, one patient died from an underlying malignancy, whereas the other patient died of myocardial infarction that occurred subsequent to bleeding at the catheter insertion site. In the urokinase group the deaths were caused by myocardial infarction and respiratory failure.

Significant differences were noted between the two groups with regard to percent lysis, length of infusion, limb salvage, and combined achievement of either pretreatment goal (Table III); t-PA was associated with shorter infusion time (20.9 hours versus 33.8 hours; $P = .001$), decrease in limb loss (8% versus 27%; $P = .03$), and increase in pretreatment-goal achievement (76% versus 50%; $P = .02$). Analysis of success in individual pretreatment-goal achievement showed t-PA and urokinase to be equivalent in unmasking stenoses (84% and 83%, respectively; P = NS), whereas t-PA was superior to urokinase in establishing run-off (81% versus 39%; $P = .001$).

Additional procedures, either operative or interventional, were required in the majority of patients (Table IV). In the urokinase group, the two additional interventional procedures required were angioplasty of a stenotic vein graft lesion and angioplasty of an anastomotic stenosis. The 20 additional operative procedures required in the urokinase patients included 1 femoral artery repair at a catheter insertion site, 4 inflow procedures, 9 outflow procedures,

Table III. Efficacy outcomes: Arterial and venous patients

Agent	*Infusion time (h)*	*Mean % lysis*	*Limb loss*	*30-d mortality*	*PTGs*		
					All PTGs	*Unmask stenosis*	*Establish run-off*
AAO							
Urokinase (n = 36)	33.8	63.7%	10 (28%)	2 (5%)	18 (50%)	30 (83%)	14 (39%)
t-PA (n = 37)	20.9	82.0%	3 (8%)	2 (5%)	28 (76%)	31 (84%)	30 (81%)
P value	.001	.03	.03		.02	NS	.001
AVO							
Urokinase (n = 23)	43	81%		0			
t-PA (n = 8)	30	77%		0			
P value	NS	NS					

PTGs, Pretreatment goals.

3 patch angioplasties of vein graft stenoses, and 3 graft replacements. In the t-PA group, the two interventional procedures after lysis included stenting of an iliac (inflow) stenosis and angioplasty of a vein graft stenosis. The 17 additional operative procedures included 1 femoral artery repair, 2 inflow procedures, 11 outflow procedures, 2 patch angioplasties, and 2 graft replacements.

Acute venous occlusion. In the group of patients receiving urokinase, six patients had upper-extremity symptoms with subclavian vein thrombosis; of these, three patients had superior vena cava involvement. Seventeen of the patients in the urokinase group had lower-extremity symptoms; of these, 12 patients had iliofemoral clot, including three with inferior vena cava involvement, whereas five patients had clot limited to the infrainguinal distribution. In the t-PA group, neither of the two patients with upper-extremity symptoms and subclavian vein thrombosis had involvement of the superior vena cava; in the patients with lower extremity symptoms, three had iliofemoral involvement, including one with caval thrombosis, and three had infrainguinal involvement only.

No significant differences were identified between the two groups with regard to any of the parameters studied, although infusion time approached significance (Table III). There were no incidents of pulmonary embolism in any of the patients studied. The two episodes of major bleeding in the urokinase group consisted of a retroperitoneal hematoma and catheter insertion site bleeding, and bleeding from the insertion site developed in one patient in the t-PA group. None of these patients required operative correction of the problem.

Additional procedures, either operative or interventional, were required in the majority of patients (Table IV). These included both procedures to deal with hemorrhage from catheter insertion sites and corrective measures to deal with the underlying problem, such as angioplasty and stenting of venous stenoses, first rib resection, and jugular turndown.

Table IV. Additional interventions required for arterial and venous occlusions

Agent	*None (%)*	*Interventional procedure (%)*	*Operative procedure (%)*
AAO			
Urokinase (n = 36)	14 (40)	2 (5)	20 (55)
t-PA (n = 37)	18 (49)	2 (5)	17 (46)
AVO			
Urokinase (n = 23)	11 (48)	12 (52)	0
t-PA (n = 8)	3 (37)	4 (50)	1 (12)

DISCUSSION

Until its removal from the marketplace in November 1998, urokinase was the agent of choice in the treatment of AVO. Its lack of availability mandates objective assessment of all potential options for patients requiring thrombolysis. t-PA has been a long-standing alternative to urokinase but has been less frequently used because of concerns over excessive bleeding risk. Many of the data on which these concerns are based, however, are drawn from studies in which dosing was higher than presently used, and in which infusions may have been prolonged as a result of less sophisticated techniques of administration. Until now, it has not been essential to examine these data critically, because urokinase was a safe, effective agent with which practitioners had vast experience. With the lack of availability of urokinase, it is now necessary to critically examine these old assumptions about the safety and efficacy of t-PA. Although limited by its retrospective nature, and although the data on venous occlusions are severely limited by the low numbers of patients in the t-PA group, this study attempts to compare the results of low-dose t-PA and standard-dose urokinase administered at a single institution over contiguous time periods. By eliminating variability based on technical advances and dosing, it is hoped that a more accurate comparison can be drawn between the safety and efficacy of these two agents than has been previously available.

The present study demonstrates that t-PA is at least equivalent to urokinase in the majority of the efficacy parameters studied (overall percent lysis, achievement of individual pretreatment goals, limb salvage, and infusion time) and that it is equivalent to urokinase in the two most

important safety parameters (major bleeding and mortality). Unfortunately, the relatively small number of patients included in the study preclude analysis of subgroups such as diabetic patients versus nondiabetic patients, sex, thrombotic versus embolic occlusion, characteristics of occluded conduit, and location of occluded vessel. Future multicenter trials will be needed to address these issues.

The inclusion of pretreatment goals in our analysis of successful outcome was undertaken to more specifically characterize successful lysis. Because thrombolysis is frequently undertaken to improve surgical or interventional options, rather than to eliminate the need for additional intervention entirely, we felt that it was important to identify whether one agent was superior to the other in achieving this end, rather than simply quantifying percent lysis. The improved limb salvage in the t-PA group is likely a major reflection of the higher rate of outflow lysis.

There are some significant pharmacologic differences between urokinase and t-PA. Urokinase is a serine protease, an endogenous form of which is present in the plasma in the form of a proenzyme with a single polypeptide chain structure (single-chain urokinase plasminogen activator or pro-urokinase).[7] This latter molecule has been manufactured by using recombinant technology (obviating the concerns over viral contamination inherent in the production of urokinase) and has had promising results in the intra-arterial treatment of acute stroke.[8] However, the degree of statistical significance achieved in this study was not sufficient to warrant Food and Drug Administration approval of the drug. Alteplase is a genetically engineered recombinant form of the mammalian protease t-PA.[9,10] t-PA is a fibrin-specific agent, whereas urokinase is not[11]. Fibrin specificity refers to the ability of an agent to preferentially bind to fibrin-bound plasminogen, as opposed to free plasminogen. Theoretically, this leads to plasminogen activation only where it is needed, in the occlusive thrombus, as opposed to indiscriminately and systemically, thus reducing the risk of hemorrhage. However, this potential benefit has not been observed in clinical practice, because both fibrin-specific and non–fibrin-specific agents are associated with systemic consumption of fibrinogen.[12]

Previous reports investigating the use of t-PA for AAO give widely varying results, most likely reflective of widely varying dosing, heparin administration, and catheter techniques. Dosing regimens ranged from 0.02 mg/kg/h to 10 mg/h, with mean total doses ranging from 5 mg to 84 mg. Use of heparin varied as well, from 0 to 1,000 units/h. Reported rates of major hemorrhage varied from 0% to 17%.[13-18] In a recently published meta-analysis of the literature on t-PA and AAO, Semba et al[19] conclude that the risk of bleeding appears to increase with increasing doses of t-PA, that the role of heparin is unclear, both in terms of safety and efficacy, and that despite the varied methods used in the different trials, t-PA appears to be associated with a safety and efficacy profile comparable with that of urokinase. In another recent retrospective meta-analysis comparing 472 patients treated for AAOs with urokinase, t-PA, and reteplase, Ouriel et al[20] reported no difference among the agents with regard to any of the important safety and efficacy parameters studied, including percent lysis, rate of major bleeding, fibrinogen nadir, and overall clinical success rate.

CONCLUSIONS

Although limited by its retrospective design, the present study produced results that are in accordance with the results of the meta-analysis by Semba et al and the more recent meta-analysis by Ouriel et al showing that t-PA is a safe and effective alternative to urokinase in the treatment of AVO. Because this study is retrospective in nature, involves consecutive time periods of study, and involves small numbers of patients, no conclusions can accurately be made regarding improved safety and efficacy of t-PA compared with urokinase. Unquestionably, a randomized controlled trial evaluating t-PA by using standardized dosing techniques and heparin administration is needed to refine our use of this agent and to further maximize its safety and efficacy.

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DISCUSSION

Dr Steven Sparks (San Diego, Calif). I would like to thank the Society for inviting me to comment on this paper and thank Dr Shortell for an excellent presentation as well as getting me the paper well in advance of the meeting.

Today she has presented to us some information about lytic therapy at the institution she represents, that is well known for being the leader in lytic therapy both in the grafts and in the venous system. What this has shown us over a 12-month time period, a retrospective analysis of urokinase versus a 21-month time period with t-PA with 36 arterial occlusions with UK and 37 with the t-PA, 23 in the urokinase for the venous and 8 for the t-PA. The main statistical advantage occurred in the arterial occlusion subgroup where the runoff was better established with the t-PA. This was trending towards slightly lower lytic therapy time periods.

I have four questions. Number one: Any analysis of these four very small groups, has a chance of a type II error built into the statistics. Do you think this is possible or probable?

Number two: Minor bleeding as the main nuisance in this procedure and the catastrophic problem with both these agents is the possibility of intracranial bleed. The overall incidence in the literature being approximately 1%. Can we really draw that the t-PA agent is safe when in your own study you had no intracranial bleeds for either agent?

Number three: Since you decrease not only the t-PA dose but also the heparin dose, which would you feel is actually primarily responsible for your decreased bleeding and your decreased complications?

Number four: Have you or anyone at your institution looked at the use of lower doses of t-PA, even lower than what you are currently using? At our own institution, we are down to about 0.02 mg/cc for lysing our grafts and we are actually opening grafts with as little as 2 mg of total t-PA use.

Thank you.

Dr Cynthia K. Shortell. Thank you, Dr Sparks. With regard to your first question, certainly I think that this is a very small group of patients. Particularly the venous group is almost as small as to be not worth including, and I agree that type II error is certainly a strong possibility.

With regard to the intracranial hemorrhage issue, I think that the incidence of ICH remains a major problem for us. It is the real bugaboo of thrombolytic therapy, and I do not know whether we can draw any conclusions from this study since there were no instances of ICH in this study. In my experience, the incidence of ICH is a sporadic event, and I think, as we discussed informally, may reflect the thrombolytic agent being in the wrong place at the wrong time, so to speak, while an event is going on or an unrecognized defect in the brain exists rather than an effect of the lytic agent itself, although the cardiac literature may belie this a little bit. In any event, I think the vascular literature suggests that the rate of ICH is probably equivalent for all of the lytic agents. I do not think we can make any conclusions from this study about the incidence of ICH.

I agree with you that the reduction in our heparin dose, while it probably has very little effect on the efficacy end of things, may have just as much or maybe even more effect on the safety end of the t-PA patients compared with UK patients, although we used the same dose of heparin in both groups of patients for the time period studied. We have actually gone to an even lower dose of heparin in many patients, sometimes even as low as 250 units IV/hour in patients undergoing thrombolysis now. I think there is evidence that this is probably even better than 500.

We have not had a lot of experience with very low dose t-PA. The little experience that we have has not been all that favorable. We seem to need that minimum of 0.05 mg/kg/hour in order to gain efficacy, but we are certainly open to suggestion and will consider the possibility of using even lower doses of t-PA in the future.

Thank you.