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Recombinant Tissue-Type Plasminogen Activator Versus a Novel Dosing Regimen of Urokinase in Acute Pulmonary Embolism: A Randomized Controlled Multicenter Trial

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Thrombolysis of acute pulmonary embolism can be accomplished more rapidly and safely with 100 mg of recombinant human tissue-type plasminogen activator (rt-PA) (Activase) than with a conventional dose of urokinase (Abbokinase) given as a 4,400-U/kg bolus dose, followed by 4,400 U/kg per h for 24 h. To determine the effects of a more concentrated urokinase dose administered over a shorter time course, this trial enrolled 90 patients with baseline perfusion lung scans and angiographically documented pulmonary embolism. They were randomized to receive either 100 mg/2 h of rt-PA or a novel dosing regimen of urokinase: 3 million U/2 h with the initial 1 million U given as a bolus injection over 10 min. Both drugs were delivered through a peripheral vein.

To assess efficacy after initiation of therapy, repeat pulmonary angiograms at 2 h were performed in 87 patients and then graded in a blinded manner by a panel of six investigators. Of the 42 patients allocated to rt-PA therapy, 79% showed angiographic improvement at 2 h, compared with 67% of the 45 patients randomized to urokinase therapy (95% confidence interval for the difference in these proportions [rt-PA minus urokinase] is −6.6% to 30.4%; $p = 0.11$). The mean change in perfusion lung scans between baseline and 24 h was similar for both treatments. Three patients (two treated with rt-PA and one with urokinase) had an intracranial hemorrhage, which was fatal in one.

The results indicate that a 2-h regimen of rt-PA and a new dosing regimen of urokinase exhibit similar efficacy and safety for treatment of acute pulmonary embolism.

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In a previous randomized controlled trial (1) comparing recombinant human tissue-type plasminogen activator (rt-PA) and urokinase for treatment of acute pulmonary embolism, we demonstrated that a 100-mg dose of rt-PA given over 2 h caused more rapid clot lysis and fewer bleeding complications than did a weight-adjusted 24-h infusion of urokinase approved by the Food and Drug Administration. We stated that further work was necessary to determine whether important differences existed between rt-PA and urokinase when both were given over the same 2-h time period. Several groups (2–4) amplified our cautionary note regarding lack of comparability between the 2-h rt-PA and the 24-h urokinase thrombolytic dosing regimens. We now present the results of a subsequent randomized controlled trial in which the 100-mg rt-PA dose was tested against a novel 2-h dosing regimen of 3 million U of urokinase, administered as a bolus injection of 1 million U over 10 min followed by another 2 million U as an infusion over the next 110 min. We maintained the same two principal end points: improved findings in the 2-h pulmonary angiogram and 24-h perfusion lung scan over those obtained before treatment.

Methods

Study patients. The study group comprised patients ≥18 years old who had angiographically documented pulmonary

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embolism in one or more segmental or more proximal pulmonary arteries and who manifested new symptoms <14 days previously. Of the 92 patients randomized, 2 did not receive thrombolytic therapy. One randomization envelope (rt-PA) was opened before the pulmonary angiogram was completed; results of the pulmonary angiogram were normal and pneumonia was diagnosed. Another randomization envelope (urokinase) was opened at a center that had inadvertently not restocked its study drug. Of the 90 patients who underwent thrombolysis, 2 did not have 2-h pulmonary angiograms (1 patient randomized to urokinase therapy died of ventricular fibrillation while receiving the thrombolytic infusion, and 1 patient randomized to rt-PA therapy inadvertently removed his femoral venous sheath after 15 min of treatment). One follow-up angiogram (on a patient who received rt-PA) was technically inadequate because the catheter was in the right atrium rather than the pulmonary artery.

The protocol was approved by the Food and Drug Administration and the Human Subjects Committee of each participating hospital; written informed consent for the study was obtained from all subjects. The trial was conducted between March 1988 and March 1991.

The exclusion criteria were: 1) major internal bleeding within the previous 6 months, 2) intracranial disease, 3) operation or organ biopsy in the past 10 days, 4) occult blood on stool examination, 5) hematocrit <30%, 6) severe uncontrolled hypertension, 7) severe impairment of hepatic or renal function, 8) pregnancy or lactation, 9) inability to tolerate the initial diagnostic pulmonary angiographic investigation.

Pulmonary angiography and perfusion lung scanning. After baseline ventilation-perfusion lung scanning and measurement of right atrial, right ventricular and pulmonary artery pressures, selective angiography of the appropriate (right or left) pulmonary artery was performed. When pulmonary embolism was detected in a segmental or more proximal pulmonary artery, the patient was randomized to rt-PA or urokinase therapy by opening the appropriate consecutively numbered sealed envelope. Separate treatment assignments for each hospital were generated by the use of permuted block random number sequences. Measurement of pulmonary artery pressure and pulmonary angiography were repeated immediately after 2 h of treatment; follow-up perfusion lung scanning was performed 24 h after the start of therapy.

Pharmacologic regimens. No patient received concomitant heparin therapy with the thrombolytic agent. The dose of rt-PA (Activase [Genentech]) was 100 mg infused through a peripheral vein over 2 h (50 mg/h). The dose of urokinase (Abbokinase [Abbott Laboratories]) was modified from the dosing regimen of the German Activator Urokinase Study (5) in acute myocardial infarction, which utilized 3 million U of urokinase over 90 min, of which 1.5 million U was given as an initial intravenous bolus injection. In our trial, patients allocated to urokinase therapy were premedicated with hydrocortisone (100 mg intravenously), diphenhydramine (25 to 50 mg intravenously) and acetaminophen (650 mg orally). They then received 1 million U of urokinase through a peripheral vein over 10 min followed by 2 million U over 110 min for a total dose of 3 million U over 2 h. After discontinuation of either thrombolytic agent, heparin was given (without a bolus injection) when the thrombin time or partial thromboplastin time was less than twice the control value. The average heparin dose was 1,050 U/h (range 700 to 2,500). Heparin administration was continued, on average, for 6.6 days.

Analyses of efficacy. For formal analysis, sets of pulmonary angiograms were coded and presented to a panel of six investigators, who scored them by the system used in the Urokinase Pulmonary Embolism Trial (6). Without knowledge of the patient's treatment or the timing of the angiogram selected for analysis, investigators first judged the technical adequacy of the angiogram and then assessed it qualitatively and quantitatively. For the qualitative assessment, panelists graded change within sets of angiograms from a patient as marked, moderate, slight or absent. In the quantitative scoring system (6), unilateral angiograms were graded from 0 (no clot) to 9 (massive clot), but nonocclusive filling defects in segmental vessels were not distinguished from total occlusions. Moderate-sized pulmonary embolism was given a score of 3 to 6 and generally affected two lobes; massive pulmonary embolism was given a score of 7 to 9 and affected the entire lung.

Pairs of pre- and post-treatment lung scans were also coded to prevent identification of patients, treatment received, participating institutions and the timing of the scans in relation to thrombolytic therapy. The scans were then graded as the proportion of lung not perfused. A panel of two nuclear medicine specialists scored each scan in two ways: 1) by the anteroposterior method used in Urokinase Pulmonary Embolism Trial (UPET) (6), and 2) by a new segmental method (7) that included lateral or oblique views, or both, that were not obtained as standard practice in UPET. The scans were assessed individually by each panelist using both methods. Periodic meetings of the panel were convened by a third nuclear medicine specialist to resolve by consensus any differences in scoring.

Complications. Patients were followed up for 14 days to determine whether death or recurrent pulmonary embolism had occurred and for 3 days to determine whether major bleeding had occurred. Major bleeding was defined as bleeding that required surgical control (such as laparotomy for retroperitoneal bleeding) or any intracranial bleeding. As in the Urokinase Pulmonary Embolism Trial (6), we also identified all patients who had a decrease in hematocrit of >10 percentage points.

Coagulation variables. Plasma and serum samples were taken immediately before therapy and repeated 2 h and 24 h after the start of treatment. Blood for plasma fibrinogen was drawn into citrate (13 mmol/liter) with aprotinin (250 IU/ml) to prevent in vitro fibrinogenolysis, and it was immediately

stored on ice. Plasma was collected from these samples after centrifugation and was stored at −20°C for up to 6 weeks. Plasma fibrinogen was measured by the sodium sulfite precipitation method of Rampling and Gaffney (8). Fibrin and fibrinogen degradation products were measured in serum samples according to the method of Merskey et al. (9,10).

Statistical analysis. This randomized, two-treatment study began with an initial cohort of 30 patients (15 in each treatment arm). An interim analysis of the data on the first 30 patients indicated that a 30% difference in success rates between the two treatment arms could be detected with 80 patients (40/arm) with 80% power and a two-sided level of significance of 0.05. Success was defined as any level of improvement in qualitative pulmonary angiographic scores. After the interim analysis was completed, the study size was set at 90 patients, with the expectation that data from at least 80 patients would be analyzable.

Data from the 90 patients who received any amount of drug were analyzed with use of SAS statistical software. Two patients who were randomized to treatment but received no drug were not included in the analyses. Categoric data analyses were performed with use of chi-square and Fisher exact tests (11). Analyses of continuous random variables were performed with the Wilcoxon two-sample test (12). Confidence intervals for the differences in proportions were calculated with a normal approximation for the comparison of independent binomial samples (13). Reported p values are two-sided.

Results

The patients in the rt-PA and urokinase groups were well matched for baseline characteristics, with no statistically significant difference in any variable that was assessed (Table 1). Two hours after the start of therapy, there were no significant changes in hemodynamic variables (Table 2).

Efficacy. The proportion of patients showing any improvement on the qualitative pulmonary angiogram assessments was 79% (33 of 42) and 67% (30 of 45) for rt-PA and urokinase, respectively (Table 3). The 95% confidence interval for the difference in these proportions (rt-PA minus urokinase) is −6.6% to 30.4% (p = 0.11). With a more restrictive definition of response that included only moderate or marked improvement (Fig. 1), the proportion of responses was 33% (14 to 42) and 42% (19 to 45) for rt-PA and urokinase, respectively (Table 3). The 95% confidence interval for the difference in these proportions (rt-PA minus urokinase) is −29% to 11.4% (p = 0.39). Patients in the two treatment groups were also compared with respect to the proportion showing any improvement in the quantitative angiographic scores after treatment (Table 4). Patients treated with rt-PA had a 22.4% improvement in quantitative scores compared with 17.8% improvement among those receiving urokinase. The 95% confidence interval for the difference in the proportions (rt-PA minus urokinase) is −12.3% to 21.3% (p = 0.60). Among the 35 patients with massive pulmonary embolism (pretreatment score ≥7) and 2-h angiograms, there was no significant difference between the effect of rt-PA and urokinase (p = 0.74).

Table 1. Baseline Characteristics of 90 Patients

	rt-PA–Treated (n = 44)	Urokinase-Treated (n = 46)
Age (yr)	58.6 ± 16.6	60.1 ± 17.6
Men	26	27
Women	18	19
Symptom duration		
0 to 5 days	34	31
6 to 10 days	8	9
11 to 14 days	2	6
Prior DVT or PE	15	20
Cancer	9	12
Operation 11 to 30 days previously	7	9
Heart rate (beats/min)	87.6 ± 16.1	91.8 ± 19.2
Respiratory rate (breaths/min)	23.5 ± 7.5	23.3 ± 5.6
Pressures (mm Hg)		
Systolic	128.2 ± 21	125.3 ± 17
Diastolic	76.6 ± 11.1	78.1 ± 11.5
RA	8.5 ± 5.2	9.4 ± 5.1
RV, systolic	44.1 ± 17.6	39.4 ± 11.3
RV, diastolic	9.5 ± 7.9	9.4 ± 5.6
PA, systolic	47.4 ± 19	44.3 ± 13.1
PA, diastolic	19.1 ± 10.9	17.2 ± 7.2
PA, mean	27.8 ± 13.6	28.5 ± 9.3

Data are expressed as number of patients or mean value ± SD. DVT = deep venous thrombosis; PA = pulmonary artery; PE = pulmonary embolism; RA = right atrial; rt-PA = recombinant tissue-type plasminogen activator; RV = right ventricular.

The improvement in lung scan perfusion at 24 h was similar in the two treatment groups whether the anteroposterior (p = 0.92) or segmental (p = 0.80) scoring method was used (Table 5). The interval from the onset of symptoms to the start of thrombolytic therapy (0 to 5 vs. 6 to 14 days), the presence of cancer and a prior history of pulmonary embolism or deep venous thrombosis did not influence the efficacy of either rt-PA or urokinase, as assessed by the 2-h angiogram or the 24-h perfusion scan.

Complications. Of the 90 patients who underwent thrombolysis, 3 died within 14 days of treatment. A 78-year old woman with a prior myocardial infarction received urokinase and developed refractory ventricular fibrillation during the infusion. Autopsy was not performed and pulmonary embolism was considered the cause of death. A 55-year old woman with metastatic breast carcinoma received rt-PA and died on the following hospital day. Autopsy revealed extensive intravascular adenocarcinoma that had embolized to pulmonary and hepatic vessels. Although thrombus in the deep veins of the right leg was identified, there was no evidence of concomitant thrombotic pulmonary embolism. An 81-year old man previously in good health received rt-PA and vomited 75 min after completion of the infusion. He became comatose 2.5 h later; computed tomographic scanning of the head showed a massive subarachnoid and intracerebral hemorrhage. He died 3 days after treatment.

Table 2. Hemodynamic Changes in 96 Patients

	rt-PA		Urokinase	
	Before	After*	Before	After*
Heart rate (beats/min)	87.6 ± 16.1	82.5 ± 12.7	91.8 ± 19.2	91 ± 17.9
Mean respiratory rate (breaths/min)	25.5 ± 7.5	22.8 ± 7.6	23.3 ± 5.6	22.1 ± 5
Pressures (mm Hg)				
Systolic	128.2 ± 21	129.6 ± 21.8	125.3 ± 17	125 ± 16.1
Diastolic	76.6 ± 11.1	76.3 ± 12.6	78.1 ± 11.5	76.1 ± 11
PA, systolic	47.4 ± 19	44.2 ± 15.2	44.3 ± 13.1	43.2 ± 12.1
PA, diastolic	19.1 ± 10.9	19 ± 10.4	17.2 ± 7.2	19 ± 6.3
PA, mean	27.8 ± 11.6	28.1 ± 12	28.5 ± 9.3	28.3 ± 8.2

*Two hours after the start of therapy. Data are expressed as mean value ± SD. Abbreviations as in Table 1.

Two patients treated with urokinase experienced recurrent pulmonary embolism that was documented with new perfusion lung scan defects and managed with placement of an inferior vena cava filter. Another patient treated with urokinase was considered clinically to have recurrent pulmonary embolism and had a filter placed without undergoing repeat lung scanning or pulmonary angiography. All three of these patients were receiving intravenous heparin when recurrent pulmonary embolism was diagnosed.

Two patients had a nonfatal intracranial hemorrhage, documented by computed tomographic scan of the head, that resulted in permanent but minor neurologic disability. A 72-year old woman with three prior "spells" of "vision turning black," but none within the year before acute pulmonary embolism, received rt-PA. Five hours after termination of the infusion, aphasia and right-sided weakness were noted. She was sent to a rehabilitation facility for 6 weeks and was then discharged with minor residual neurologic deficits. A 67-year old man was transferred to a participating hospital for evaluation of delirium and new onset grand mal seizures. Ten days after transfer, pulmonary embolism was diagnosed and he was enrolled in the study (a protocol violation because of new onset of seizures and new mental status changes). He received urokinase and was noted 2 days later to have a new right homonymous hemianopia that has not resolved.

With respect to other complications of thrombolytic therapy (Table 6), eight patients who received urokinase had an allergic reaction, usually characterized by rigors, compared with no patient treated with rt-PA ($p = 0.004$). The frequency of major bleeding complications was similar in both treatment groups. Twelve patients had a hematocrit decrease >10 percentage points and 11 received blood transfusions. Four of the 12 had no obvious source of bleeding to explain the decrease in hematocrit. Of the eight patients with an identified bleeding site, the groin puncture site for pulmonary angiography accounted for the decreased hematocrit in seven patients and an unsuspected abdominal aortic aneurysm that ruptured accounted for the decrease in one patient; this aneurysm was later successfully repaired.

Coagulation variables. Nadir fibrinogen levels were observed at 2 h after initiation of thrombolytic therapy and exceeded 100 mg/dl in all patients. The difference between the nadir level and the baseline plasma fibrinogen level (Table 7) was not significantly different between the two treatment groups ($p = 0.43$). Greater than average percent decreases in plasma fibrinogen did not identify patients with major bleeding. There was no significant difference in fibrinogen degradation products between treatment groups ($p = 0.64$).

Table 3. Qualitative Angiographic Assessment in 87 Patients

Change	rt-PA (n = 42)	Urokinase (n = 45)
Marked improvement	5 (12%)	4 (9%)
Moderate improvement	9 (22%)	15 (33%)
Slight improvement	19 (45%)	11 (24.5%)
No change	6 (14%)	12 (27%)
Slightly worse	3 (7%)	2 (4.5%)
Moderately worse	0	0
Markedly worse	0	1 (2%)

Abbreviation as in Table 1.

Discussion

Recombinant human tissue-type plasminogen activator and urokinase. These agents are serine proteases that have similar structural and catalytic properties (14). We found that a 2-h infusion of 100 mg of rt-PA or 3 million U of urokinase provided comparable efficacy and safety. The two agents lysed thrombus rapidly and had a similar likelihood of causing hemorrhage. Quantitative angiographic assessment at 2 h without controlling for baseline values revealed a statistically nonsignificant trend favoring rt-PA over urokinase ($p = 0.16$). This trend was also seen with the qualitative angiographic assessment (which evaluated change relative to baseline at 2 h) and was also not statistically significant ($p = 0.11$). However, with control for baseline values, the quantitative angiographic assessment at 2 h showed no trend favoring rt-PA and differences between results with the two agents were not statistically significant ($p = 0.60$). The

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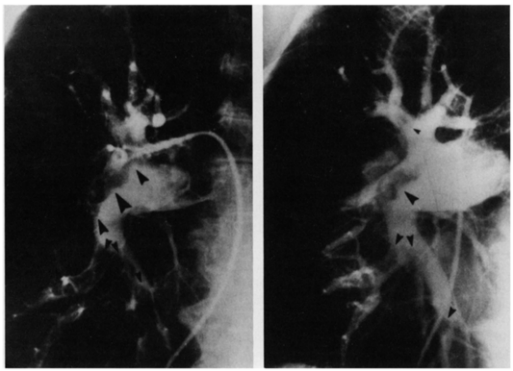

Figure 1. Left panel, Right pulmonary angiogram reveals multiple emboli (**arrowheads**) in the upper, middle and lower lobe arteries. **Right panel,** Repeat angiogram immediately after administration of urokinase was scored as showing moderate overall improvement with significantly decreased thrombus, particularly in the upper and lower lobe arteries, although residual thrombus (**arrowheads**) is present.

Table 4. Quantitative Angiographic Assessment

Score	rt-PA (n = 42)	Urokinase (n = 45)
Pretreatment	6.04 ± 2.23	6.43 ± 2.05
Post-treatment	4.69 ± 2.15	5.29 ± 2.21

Definition of Scores

Lesion	Score
1. Segmental vessel with filling defect or obstruction	1
2. Upper lobe vessel	
With filling defect	2
With obstruction	3
Maximal score for vessel	3
3. Middle lobe vessel (including lingular vessel)	
With filling defect or obstruction	2
Maximal score for vessel	2
4. Lower lobe vessel	
With filling defect	2
With obstruction	4
Maximal score for vessel	4
5. Main pulmonary artery	
Obstruction of either	9*
Obstruction of intermediate artery on either side	6†
6. Total score >9	9
7. Total score ≤4 for a lung with a filling defect in the pulmonary trunk, pulmonary artery or intermediate artery‡	Total lung score +5

*Based on total score for upper, middle and lower lobe obstructions (i.e., 3 + 2 + 4 = 9). †Based on total score for middle and lower lobe obstructions (i.e., 2 + 4 = 6). ‡A total lung score ≤4 mandates a check for such filling defects. Pre- and post-treatment scores are expressed as mean value ± SD. Abbreviation as in Table 1.

magnitude of the observed difference between rt-PA and urokinase in the quantitative angiographic assessment controlling for baseline values would require a 1,250-patient study to detect a statistically significant difference between treatments with 70% power and a two-sided p value of 0.05. The improvement in perfusion lung scans at 24 h was virtually identical in both groups.

Characteristics of the novel urokinase dosing regimen. When we compare the urokinase results in our current and previous (1) trials, the novel 2-h urokinase regimen appears to act more rapidly and to be safer than the 24-h regimen; 66% of patients demonstrated angiographic improvement at 2 h compared with 48% who attained this end point in our previous study. Marked or moderate improvement with urokinase occurred in 42% of patients who received 3 million U/2 h compared with 13% who received an average weight-adjusted dose of 1 million U/2 h in the previous study. Lung scan reperfusion 24 h after initiation of urokinase was similar in the two trials, even though the total amount of drug administered was much less in the current study (3 million U

Table 5. Perfusion Lung Scan Assessment

	rt-PA	Urokinase
Anteroposterior method		
Pretreatment	0.312 ± 0.153	0.342 ± 0.189
Post-treatment	0.221 ± 0.139	0.252 ± 0.16
Segmental view method		
Pretreatment	0.375 ± 0.156	0.404 ± 0.22
Post-treatment	0.27 ± 0.17	0.31 ± 0.18

Data are expressed as mean value ± SD of the proportion of lung not perfused. Abbreviation as in Table 1.

versus an average of 7.5 million U). The frequency of a >10-point decrease in hematocrit was reduced from 48% of patients with the 24-h regimen to 6.5% with the 2-h regimen.

The fixed 2-h dosing regimen of urokinase was much more manageable than the previously administered weight-adjusted 24-h infusion. With this novel dosing schedule, only 40% as much urokinase was utilized, resulting in a substantial reduction in cost. However, even with aggressive triple drug premedication, allergic reactions occurred in 17% compared with 26% of patients who received urokinase in the prior study. Theoretically, the ongoing development of recombinant urokinase should eliminate this problem.

The success of our urokinase regimen, in which one third of the total dose was given as a bolus injection, was consistent with the findings in a canine model of venous thrombosis (15) in which a bolus injection/infusion ratio of 25%/75% of urokinase produced twice as much lysis as either the bolus injection or infusion alone. One can speculate that the improved results with 3 million U/2 h are due in part to saturation with this more concentrated dosing regimen of the recently described plasminogen activator inhibitor 3 (PAI-3).

Prior studies. The results of our previous trial (1) with 100 mg/2 h of rt-PA were almost identical to those of the present study. In these two studies with the same rt-PA dosing regimen, angiographic evidence of clot lysis at 2 h was obtained in 80% (95% confidence interval 70% to 90%) of patients. Lung scan reperfusion at 24 h was virtually the same (28% to 29%) in the two trials. A hematocrit decrease of ≥10 percentage points was observed in 17% (95% confidence interval 8% to 26%) of patients treated with rt-PA.

When the frequency of qualitative angiographic improvement in the two groups treated with rt-PA is combined and then compared with that in the patients receiving the 2-h urokinase regimen, the 95% confidence interval for the difference in the proportion responding (rt-PA minus urokinase) is −4% to 30% (p = 0.12). If only moderate or marked angiographic improvement is considered, the 95% confidence interval for the difference in the proportion with moderate or marked improvement is −19% to 19% (p = 0.98).

The lack of reduction in pulmonary artery pressure despite successful fibrinolysis in most patients is surprising and not readily explained. In our prior open label (16) and randomized (1) trials of thrombolysis in pulmonary embolism, a decrease in pulmonary artery pressure was common and usually indicated that therapy succeeded.

At first glance, our results may appear to conflict with those reported by Prewitt et al. (17) in their canine model of pulmonary embolism. They compared two doses of rt-PA (1 and 2 mg/kg) with two doses of urokinase (30,000 and 60,000 U/kg) and found that both rt-PA regimens yielded more extensive thrombolysis than did either of the urokinase dosing schedules. However, the canine and human fibrinolytic systems may differ and all four of their treatment regimens were 15-min (rather than 2-h) infusions. They demonstrated in a previous study (18) in dogs that compressing the rt-PA dosing regimen from 90 to 15 min results in a markedly increased rate of clot lysis.

Table 6. Complications Associated With Therapy in 90 Patients

	rt-PA (n = 44)	Urokinase (n = 45)
Allergy	0	8
Intracranial bleeding	2	1
Gastrointestinal bleeding	1*	1†
Hematocrit decrease >10 percentage points	7	5
Blood transfusion	6	5
Reasons for transfusion		
Shock	1	1
Augmentation of hematocrit	5	4
Amount of blood transfused		
1 unit	3	1
2 units	2	3
3 units	1	0
13 units	0	1‡

*Mallory-Weiss tear. †Occult blood in stool; source not determined. ‡Ruptured abdominal aortic aneurysm (successfully repaired surgically) in a patient who became symptomatic approximately 18 h after initiation of the thrombolytic infusion. Abbreviation as in Table 1.

Optimizing safety. Although both 2-h regimens caused clot lysis in most patients, important bleeding complications occurred. The intracranial hemorrhage rate was 3% overall, including a 1% rate of fatal intracranial bleeding. The lack of episodes of intracranial bleeding in our prior studies was undoubtedly due to the small number of patients and the play of chance. When our total experience with thrombolysis in pulmonary embolism (1,16,19) is considered, the overall rate of intracranial bleeding is 1.6%, including a 0.5% rate of fatal bleeding. These findings emphasize the need for careful patient selection.

In 13% of patients in the current trial, the hematocrit decreased >10 percentage points. In two thirds of cases, this decrease was due to bleeding from the pulmonary angiogram groin puncture site. This observation underscores the need for meticulous attention to technical aspects of performing pulmonary angiograms, especially with regard to the initial percutaneous puncture of the femoral vein (20). We believe that our insistence on the use of pigtail- or balloon-tipped

Table 7. Laboratory Indexes of Fibrinolysis

	rt-PA	Urokinase
Fibrinogen (mg/dl)		
0 h	464.1 ± 140.9	426.5 ± 174.8
2 h	312.6 ± 168	236.1 ± 119
24 h	366.5 ± 158	267.1 ± 128.6
FDP (μg/ml)		
0 h	3.3 ± 16.4	0.7 ± 1.5
2 h	75.7 ± 158.6	44.9 ± 155.1
24 h	6.9 ± 22.4	6.2 ± 21.9

Data are expressed as mean value ± SD. FDP = fibrinogen degradation products; other abbreviation as in Table 1.

catheters for pulmonary artery catheterization was responsible for the absence of episodes of right ventricular perforation and pericardial tamponade.

Future studies. Experimental (21) and clinical (22) reports suggest that thrombolysis in pulmonary embolism can be achieved with improved safety and equivalent efficacy by compressing the infusion into 2 to 15 min, administering a weight-adjusted rather than a fixed dose of drug and reducing the total dose of rt-PA. The theory is that soluble, cross-linked fibrinogen degradation products derived from lysis of thrombi causing pulmonary embolism circulate in the plasma and may act as a cofactor similar to fibrin in promoting the conversion of plasminogen to plasmin when rt-PA is infused continuously (21). However, after bolus administration, rt-PA is cleared rapidly and only small amounts of circulating rt-PA are available to interact with cross-linked fibrinogen degradation products, thereby limiting the potential to activate plasma plasminogen and to promote systemic fibrinogenolysis.

To test this hypothesis, we are initiating an international, multicenter, randomized trial comparing bolus injection of rt-PA (0.6 mg/kg with a maximal dose of 50 mg administered over 15 min) with the 100-mg/2 h dose of rt-PA approved by the Food and Drug Administration. However, to address the circumstances under which thrombolysis followed by anticoagulation should be administered for pulmonary embolism instead of anticoagulation alone, a future trial with a sample size of many hundreds of patients will be required to study clinical (rather than radiologic imaging) end points such as mortality and recurrent pulmonary embolism.

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