Tissue Plasminogen Activator (rt-PA) vs Heparin in Deep Vein Thrombosis*

Results of a Randomized Trial


We performed a randomized trial comparing two dosing regimens of recombinant tissue plasminogen activator (rt-PA) plus heparin vs heparin alone in the treatment of acute proximal deep vein thrombosis in 83 patients. Of 12 patients who received 0.5 mg/kg rt-PA plus heparin over 4 h, seven (58 percent) had greater than 50 percent lysis of the thrombus, compared with none of 12 who received placebo plus heparin (p = 0.002). Of 28 patients who received 0.5 mg/kg rt-PA over 8 h, repeated in 24 h, six (21 percent) had greater than 50 percent lysis, compared with two (7 percent) of 30 patients who received placebo plus heparin (p = 0.11). The 4-h infusion of rt-PA produced a 40 percent reduction and the 8-h infusion an 11 percent reduction in plasma fibrinogen concentration. At long-term follow-up, three (25 percent) of 12 patients in whom greater than 50 percent lysis was achieved had symptoms of the postphlebitic syndrome, compared with 19 (56 percent) of 34 patients in whom lysis was less than 50 percent (p = 0.07).

Anticoagulant therapy is the standard treatment for patients with venous thrombosis; it is used in over 90 percent of such patients treated in North America. Anticoagulant therapy is highly effective in preventing thrombus extension or embolization but does not produce significant thrombolysis, and its use is associated with an appreciable rate of the postphlebitic syndrome. Thus, as many as two thirds of patients with deep vein thrombosis (DVT) who are treated with heparin experience loss of venous valve function and alteration of venous return, and more than half of all patients with proximal vein thrombosis develop symptoms of chronic venous insufficiency. Thrombolytic therapy induces lysis of thrombi and therefore has the potential to prevent venous valve damage and reduce the incidence of the postphlebitic syndrome. Although streptokinase (SK) and urokinase have been approved for the treatment of DVT for almost 20 years, heparin has remained the mainstay of acute therapy, mainly because of concern about hemorrhage with thrombolytic agents and uncertainty as to their effectiveness in preventing the postphlebitic syndrome.

Streptokinase therapy has been evaluated in a number of small studies in patients with DVT and has been shown to produce greater lysis of thrombi than heparin when findings on repeat venography are used as the primary outcome measure. A pooled analysis of the six randomized trials indicated that in patients treated with SK, significant lysis was achieved 3.7 times more often than patients treated with heparin, but with a threefold increase in the risk of bleeding. However, none of the trials was large enough to establish conclusively the efficacy or safety of SK relative to that of anticoagulant therapy.

Recently there has been increased interest in the clinical use of thrombolytic agents, due primarily to the impressive clinical results of thrombolysis in patients with acute myocardial infarction and to the development of recombinant tissue-type plasminogen activator (rt-PA), which appears to be more effective than SK in lysing coronary artery thrombi. We therefore performed a double-blind randomized trial in patients with acute proximal DVT and tested two different dosage regimens of rt-PA to determine if thrombolysis can be achieved without producing fibrinogenolysis. In addition, we performed long-term follow-up on all available patients to determine the relationship between thrombolysis and the development of clinical manifestations of the postphlebitic syndrome.

Materials and Methods

Subjects

Patients less than 75 years old with venographically confirmed proximal DVT of the lower limbs and symptoms of less than seven days' duration were eligible for entry into the study. Patients were excluded if they had an underlying bleeding disorder, active peptic ulcer disease, active bleeding process, cerebrovascular accident or other intracranial process within two months, or had undergone major surgery, major trauma, obstetric delivery, organ biopsy, or puncture of a noncompressible vessel within seven days. The study protocol was approved by the Institutional Review Boards of the participating hospitals and informed consent was obtained from all patients before randomization.

Protocol

Both two-chain and one-chain rt-PA (Genentech, South San Francisco, CA) were used in the study. All patients received an initial intravenous (IV) heparin bolus of 5,000 U followed by a
heparin infusion administered at a starting dose of 30,000 U/24 h and adjusted to maintain the activated partial thromboplastin time (APTT) at 1¼ to 2 times control.

The study was performed in two phases. In phase I, 24 patients were randomly allocated to treatment with two-chain rt-PA, 0.5 mg/kg infused IV over 4 h, or an identical-appearing placebo. In phase II, 59 patients were randomly allocated to one-chain rt-PA, 0.5 mg/kg (except for two patients who received two-chain rt-PA) infused over 8 h and repeated in 24 h, or an identical-appearing placebo regimen.

Heparin was continued during the study drug infusion, then continued for seven to ten days, and followed by oral anticoagulant therapy with warfarin, the dose of which was adjusted to maintain the International Normalized Ratio (INR) at 2.0 to 3.0. Warfarin was continued for three months.

Blood was collected before and after the rt-PA infusion to determine levels of plasma fibrinogen, α1-antiplasmin, and fibrinogen degradation products (FDPs). In addition, APTT, thrombin clotting time, and prothrombin times were assayed. The blood was centrifuged at 1,600 g for 15 min at room temperature, divided into aliquots, and frozen at −70°C for batch assay.

Outcome Assessments

THROMBOLYSIS. The effectiveness of the treatment regimens in producing thrombolysis was assessed with repeat venography at 24 to 48 h after randomization. The venograms were assessed to determine the number of patients in each group who showed a clinically important improvement, defined as thrombolysis of 50 percent or more from baseline, which was the primary outcome measure (Fig 1). The venograms were interpreted by an independent panel without knowledge of the clinical findings or the treatment group to which any patient had been assigned.

HEMORRHAGE. Each patient was carefully assessed for symptoms and signs of bleeding over the initial 24 h of treatment, and then daily. Bleeding was classified as major if it was clinically overt and associated with a fall in hemoglobin of 2 g/dl or more, if it led to a transfusion of two or more units of blood, or if it was retroperitoneal, intracranial, intraocular, or intra-articular. Bleeding was defined as minor if it was clinically overt but did not meet the other criteria for major bleeding.

LONG-TERM FOLLOW-UP. Patients were seen two to three years post treatment for follow-up and evaluated by an investigator blinded to the original treatment regimens. Patients who complained of persistent (greater than one month's duration) pain and swelling of the legs and who had evidence of reflux on Doppler ultrasonography were considered to have the postphlebitic syndrome.

RESULTS

Patient Population

Of the 24 patients in phase I of the study, 12 received rt-PA and 12 received placebo. Fifty-nine patients were recruited to phase II; 29 received rt-PA and 30 received placebo.

Outcome Assessments

THROMBOLYSIS. The results obtained with the two treatment regimens and with placebo are compared...
Table 1—Thrombolysis with rt-PA, 0.5 mg/kg over 4 h, or Placebo as Evaluated by Venography

<table>
<thead>
<tr>
<th>Lysis</th>
<th>rt-PA (n = 12)</th>
<th>Placebo (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2—Thrombolysis with rt-PA, 0.5 mg/kg over 8 h × 2, or Placebo as Evaluated by Venography

<table>
<thead>
<tr>
<th>Lysis</th>
<th>rt-PA (n = 29)</th>
<th>Placebo (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>No repeat</td>
<td>1</td>
<td>-</td>
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In Tables 1 and 2. In phase I, of the 12 patients who received 0.5 mg/kg of rt-PA plus heparin over 4 h, greater than 50 percent lysis of thrombus was achieved in seven (58 percent). Of the 12 patients who received placebo plus heparin, none had greater than 50 percent lysis. The between-group difference in the proportion of patients who had greater than 50 percent lysis was statistically significant (p = 0.002). In phase II, of the 28 patients who received rt-PA, 0.5 mg/kg infused over 8 h, repeated in 24 h, and who underwent follow-up venography, greater than 50 percent lysis was achieved in six (21 percent), compared with two (7 percent) of the 30 patients who received placebo plus heparin. The between-group difference in the proportion of patients who had greater than 50 percent lysis favored rt-PA but was not statistically significant (p = 0.11). For phases I and II combined, the regimen of 0.5 mg/kg of rt-PA appeared to cause more lysis than heparin, but the difference in effectiveness was not quite statistically significant (p = 0.09).

Hemorrhage. Two patients who received 0.5 mg/kg rt-PA over 4 h had overt bleeding, one with marked subcutaneous ecchymosis and one who developed hemorrhagic ten days after an elective hip replacement. In two other patients the hemoglobin fell more than 2 g/dl without evidence of overt bleeding. Of the patients in phase II who received 0.5 mg/kg rt-PA over 8 h, repeated once, one patient had significant subcutaneous ecchymosis. In the groups that received placebo plus heparin, one patient had a spontaneous hemorrhasia involving the shoulder and in one patient the hemoglobin fell more than 2 g/dl without overt bleeding.

Laboratory Tests. The 4-h infusion of rt-PA, 0.5 mg/kg, produced a mean plasma fibrinogen concentration of approximately 60 percent of the preinfusion value, a fall in α₂-antiplasmin to almost undetectable levels, and a fourfold increase in the serum FDP concentration (Table 3). In contrast, in the patients who received rt-PA, 0.5 mg/kg over 8 h, there was an 11 percent reduction in mean plasma fibrinogen concentration, a 36 percent reduction in mean α₂-antiplasmin levels, and only a moderate increase in serum FDP concentration (Table 4).

Long-term Follow-up. Long-term follow-up was possible in 46 patients; of the other 37 patients, 22 had died and 15 were not readily available for follow-up. Of these 46 patients, seven received heparin plus rt-PA, 0.5 mg/kg over 4 h; 20 received heparin plus rt-PA, 0.5 mg/kg over 8 h; and 19 received heparin and placebo. Greater than 50 percent lysis was achieved in 12 patients: in five with 0.5 mg/kg rt-PA infused over 4 h; in five with 0.5 mg/kg rt-PA infused over 8 h, repeated once, and in two with placebo. Three (25 percent) of the 12 patients in whom greater than 50 percent lysis was achieved had symptoms of the postphlebitic syndrome, compared with 19 (56 percent) of 34 in whom less than 50 percent or no lysis was achieved (NS, p = 0.07).

Table 3—Indices of Lytic Activity after 4-h Infusion of rt-PA, 0.5 mg/kg (Mean ± SD)*

<table>
<thead>
<tr>
<th></th>
<th>rt-PA</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.62 (1.9)</td>
<td>2.86 (2.05)</td>
</tr>
<tr>
<td>α₂-Antiplasmin, %</td>
<td>0.96 (0.19)</td>
<td>0.26 (0.27)</td>
</tr>
<tr>
<td>FDP, g/L</td>
<td>0.050 (0.070)</td>
<td>0.200 (0.100)</td>
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*FDP = fibrin(ogen) degradation products.

Table 4—Indices of Lytic Activity after 8-h Infusion of rt-PA, 0.5 mg/kg (Mean ± SD)*

<table>
<thead>
<tr>
<th></th>
<th>rt-PA</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.23 (1.39)</td>
<td>3.75 (1.35)</td>
</tr>
<tr>
<td>α₂-Antiplasmin, %</td>
<td>1.06 (0.13)</td>
<td>0.69 (0.17)</td>
</tr>
<tr>
<td>FDP, g/L</td>
<td>0.041 (0.051)</td>
<td>0.182 (0.287)</td>
</tr>
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</table>

*FDP = fibrin(ogen) degradation products.
DISCUSSION

In this study, two-chain rt-PA administered over 4 h produced lysis of proximal DVT more often than heparin. The rate of lysis achieved at the higher concentration of rt-PA administered over 4 h is similar to that reported in previous studies using SK administered over 48 to 72 h. Because thrombolysis with this rt-PA regimen was associated with a significant fall in plasma fibrinogen concentration, we decided to perform the second phase using a lower concentration but a greater total dose to determine whether effective thrombolysis could be achieved with rt-PA without inducing a systemic fibrinolytic state. Although the regimen used in the second phase produced only a slight fall in fibrinogen, induced thrombolysis was not significantly better than with placebo. Thus, in patients with DVT clinically important thrombolysis could be achieved with rt-PA without inducing a systemic fibrinolytic state.

In this study, the overall prevalence of the postphlebitic syndrome was 48 percent at three year follow-up. The data suggest, based on a nonsignificant trend (p = 0.07), that the incidence of the postphlebitic syndrome is lower in patients in whom greater than 50 percent lysis is achieved, an observation consistent with reports from other small studies of thrombolysis with SK.

However, a large-scale clinical trial with a higher dose of rt-PA is required to answer the major remaining question in the treatment of DVT: Does effective thrombolysis reduce the frequency of the postphlebitic syndrome?

REFERENCES