A Prospective, Randomized Trial Comparing Combination Half-Dose Tissue-Type Plasminogen Activator and Streptokinase With Full-Dose Tissue-Type Plasminogen Activator

Cindy L. Grines, MD; Steven E. Nissen, MD; David C. Booth, MD; John C. Gurley, MD; Noah Chelliah, MD; Richard Wolf, MD; James Blankenship, MD; Marcelo C. Branco, MD; Kim Bennett, RN; Anthony N. DeMaria, MD; and the Kentucky Acute Myocardial Infarction Trial (KAMIT) Group

Background. The potential benefits of combination thrombolytic agents in the treatment of myocardial infarction remain uncertain. In a small pilot study, we demonstrated that combining half-dose tissue-type plasminogen activator (t-PA) with streptokinase (SK) achieved a high rate of infarct vessel patency and a low rate of reocclusion at half the cost of full-dose t-PA.

Methods and Results. We designed a prospective trial in which 216 patients were randomized within 6 hours of myocardial infarction to receive either the combination of half-dose (50 mg) t-PA with streptokinase (1.5 MU) during 1 hour or to the conventional dose of t-PA (100 mg) during 3 hours. Acute patency was determined by angiography at 90 minutes, and angioplasty was reserved for failed thrombolysis. Heparin and aspirin regimens were maintained until follow-up catheterization at day 7. Acute patency was significantly greater after t-PA/SK (79%) than with t-PA alone (64%, p<0.05). After angioplasty for failed thrombolysis, acute patency increased to 96% in both groups. Marked depletion of serum fibrinogen levels occurred after t-PA/SK compared with t-PA alone at 4 hours (37±36 versus 199±66 mg/dl, p<0.0001) and persisted 24 hours after therapy (153±66 versus 252±75 mg/dl, p<0.0001). Reocclusion (3% versus 10%, p=0.03), infarct reinfarction (0% versus 4%, p<0.05), and need for emergency bypass surgery (1% versus 6%, p=0.05) tended to be less in the t-PA/SK group. Greater myocardial salvage was apparent in the t-PA/SK group as assessed by infarct zone function at day 7 (−1.9 SD/chord versus −2.3 SD/chord after t-PA alone, p<0.05). In-hospital mortality (6% versus 4%) and serious bleeding (12% versus 11%) were similar between the two groups.

Conclusions. These results suggest that a less expensive regimen of half-dose t-PA with SK yields superior 90-minute patency and left ventricular function and a trend toward reduced reocclusion compared with the conventional dose of t-PA. (Circulation 1991;84:540–549)

The objectives of thrombolytic therapy are to rapidly restore coronary patency, to prevent reocclusion, to salvage myocardium, and, thereby, to enhance survival. Of the thrombolytic agents currently available, each has intrinsic advantages and limitations when used individually. Although tissue-type plasminogen activator (t-PA) has been demonstrated to be more effective than streptokinase at initially achieving infarct vessel patency,1,2 its short half-life may result in an increased rate of reocclusion and recurrent ischemic events.3-5 Recent studies suggested that substituting longer-acting, systemic fibrinolytic agents for the t-PA maintenance infusion reduces the rate of reocclusion with no additional risk of bleeding.6-8 In a small pilot study, we demonstrated that the combination of half-dose t-PA with full-dose streptokinase offered high infarct vessel patency and a low rate of reocclusion.8 To assess the precise comparability of our combination regimen to full-dose t-PA, a randomized prospective trial entitled the Kentucky...
Acute Myocardial Infarction Trial (KAMIT) was undertaken. Our hypotheses were 1) that combining half-dose t-PA with streptokinase would produce acute patency rates similar to full-dose commercially available t-PA, 2) that reoclusion would be reduced by the systemic fibrinolytic effect of streptokinase, and 3) that relative to other thrombolytic strategies designed to maximize patency, this regimen would result in a substantial reduction in cost.

Methods

Patient Selection

Patients between the ages of 18 and 75 years who were admitted to the hospital up to 6 hours since the onset of chest pain were considered for enrollment if ST segment elevation of at least 1 mm was present in two or more contiguous electrocardiographic leads. Exclusion criteria included age greater than 75 years, prior coronary artery bypass graft surgery, acute gastrointestinal bleeding during the preceding 3 months, severe trauma or cerebrovascular accident within the last 6 months, sustained hypotension (systolic blood pressure <90 mm Hg unresponsive to volume expansion), uncontrolled hypertension (diastolic pressure >110 mm Hg by repeated measurements), and the use of streptokinase within the preceding 6 months.

Study Protocol

The treatment algorithm is demonstrated in Figure 1. Eligible patients with acute myocardial infarction were identified by one of the collaborating physicians. After informed consent was obtained, randomization was obtained by calling a 24-hour toll-free number. Patients assigned to the combination arm received one-half (50 mg) of the customary dose of commercially available t-PA administered as a 10-mg bolus followed by a 40 mg i.v. infusion during 1 hour. Streptokinase 1.5 MU (Streptase, Hoechst-Roussel) was infused concomitantly through a separate intravenous line. Patients randomized to the conventional full-dose t-PA arm received commercially available t-PA (Activase, Genentech, Inc., South San Francisco, Calif.) administered according to Federal Drug Administration guidelines of 100 mg during 3 hours (10-mg bolus followed by a 50-mg i.v. infusion during the first hour and a 20-mg i.v. infusion, successively, during the second and third hours).

Patients were transported to the cardiac catheterization laboratory immediately after initiation of thrombolytic therapy. After arterial access was obtained, heparin (3,000–5,000 units) was administered intravenously. Arteriography of infarct- and noninfarct-related arteries was performed with two to four angiograms imaged in appropriate orthogonal views 90 minutes after initiation of therapy. Identification of the infarct-related artery was based on the location of ST segment elevation on the electrocardiogram, abnormal wall motion on the ventriculogram, and residual stenosis or thrombus, or both, in the coronary artery. Infarct vessel patency was classified (grades 0–3) from the final angiogram according to the Thrombolysis in Myocardial Infarction (TIMI) study classification.

Patients with unsuccessful thrombolysis, defined as TIMI grade 0 or 1 flow, received an additional 5,000–7,000 units heparin and underwent attempted mechanical reperfusion with percutaneous transluminal coronary angioplasty (PTCA). PTCA was considered successful if a final infarct vessel stenosis of less than 70% and TIMI grade 2 or 3 flow was achieved. Patients with an initially patent infarct vessel at 90 minutes, defined as TIMI grade 2 or 3 flow, did not undergo emergency PTCA. Biplane left ventriculography was performed at the completion of the interventional procedure.

Hospital Regimen

Patients were routinely treated with lidocaine (2 mg/min), initiated before thrombolytic therapy and continued for 24 hours. Nitrate preparations and β-adrenergic blocking agents were not used routinely but were administered if clinically indicated. Aspirin (325 mg/day) and diltiazem (240 mg/day) were routinely started after cardiac catheterization. After publication of the Second International Study of Infarct Survival, some investigators chose to administer chewable aspirin in the emergency room. Blood was collected in tubes containing 0.5 ml sodium citrate before treatment and every 4 hours thereafter for measurement of serum fibrinogen. Intravenous heparin (adjusted to prolong the partial thromboplastin time 1.5–2 times normal) was initiated immediately after cardiac catheterization but temporarily

Figure 1. Study design. tPA, tissue-type plasminogen activator; SK, streptokinase; TIMI, Thrombolysis In Myocardial Infarction flow grade; ASA, aspirin.
was discontinued when fibrinogen levels were less than 100 mg/dl. Heparin was also temporarily discontinued for removal of arterial access sheaths on day 2, then resumed until hospital day 6. In the absence of unstable ischemia, necessitating urgent catheterization, patients underwent elective follow-up catheterization on day 7.

Radionuclide ventriculography was performed at rest within 24 hours of admission and repeated, both at rest and with exercise, before follow-up catheterization. Cardiac medications were not discontinued for the study. Exercise was performed with use of supine bicycle ergometer. After a 2-minute “warm-up” period at a work load of 25 W, staged exercise testing was performed with a 25-W increase in work load every 4 minutes. Exercise was continued until limited by symptoms of fatigue, chest pain, or ventricular arrhythmias. At least 1 minute was allowed to elapse for stabilization of heart rate before acquisition of exercised-gated images. Semiautomated, background-corrected time–activity curves were generated from the left anterior oblique views for determination of ejection fraction in a standard fashion.

Bleeding Complications

Vascular access sites, gastrointestinal and urinary output were examined daily for bleeding. Hematocrit levels were measured on days 1, 2, 3, and 6. Transfusion was withheld unless the hematocrit level was less than 30% or bleeding was thought to be hemodynamically significant. The site of bleeding and the need for blood transfusion were recorded for all patients. Bleeding was classified as serious if it required transfusion of one or more units of packed red blood cells or if it consisted of intracranial, retroperitoneal, or gross gastrointestinal hemorrhage.

Angiographic and Left Ventricular Analysis

All acute and follow-up coronary angiograms were reviewed independently by the operator and a second experienced angiographer (S.N.) unaware of the time of the study and the thrombolytic drug received. When the two angiographers did not agree on the perfusion status of the infarct vessel, a third angiographer (J.G.) determined coronary patency in a blind manner. Infarct vessel reocclusion was defined as the existence of a vessel that was patent (TIMI grade 2 or 3 flow) at the completion of the acute catheterization but that was occluded (TIMI grade 0 or 1 flow) at the time of follow-up angiography. Multivessel coronary artery disease was defined as a 70% or more stenosis in two or more major epicardial vessels.

The 30° right anterior oblique end-diastolic endocardial left ventricular outlines from a non–post-premature sinus beat and the outline of the grid were traced by a single technician unaware of the time of the study and study medication. With a tablet digitizer, the outlines were transferred into a Compaq Desk Pro 286 computer containing a Digisonics catheterization laboratory analysis system. Left ventricular volumes and ejection fraction were calculated with the area–length method. Regional wall motion of the infarct and noninfarct zones was determined by the centerline chord method described by Sheehan et al. Briefly, endocardial motion was measured along 100 chords drawn perpendicular to a centerline constructed midway between the end-diastolic and end-systolic contours. The measured motion of the 100 chords was normalized for heart size by dividing by the end-diastolic perimeter. For each myocardial segment analyzed, regional wall motion was calculated as the mean motion of one half of the most abnormally contracting contiguous chords and expressed in standard deviations per chord from normal. Hypokinesis was indicated by negative values and hyperkinesis by positive values. Technically inadequate ventriculograms due to ventricular arrhythmias or inadequate opacification were excluded, resulting in analysis being performed on 174 acute ventriculograms and 148 follow-up ventriculograms.

End Points

The primary end point was 90-minute patency, with secondary end points including in-hospital reocclusion, regional and global left ventricular function, bleeding complications, and recurrent ischemic events.

Statistical Analysis

Sample size calculation required 103 patients in each arm to test for a 20% difference in acute patency with a power of 80% and an alpha of 0.05, assuming an acute patency rate in either arm of 70%. Categorical variables in the two treatment groups were compared by \( \chi^2 \) analysis and continuous variables by Student's \( t \) test. Analyses were made on an intention-to-treat basis, and values are expressed as mean±SD. Differences were considered significant at \( p<0.05 \).

Results

Patient Characteristics

Between June 1988 and April 1990, 216 patients were enrolled in the study, with 109 patients randomized to receive combination t-PA/streptokinase and 107 patients randomized to full-dose t-PA. Baseline characteristics between the two groups were closely matched as demonstrated in Table 1. The average age was 54 years, 83% of the population was male, and the index infarct location was anterior in 42% of patients. The incidence of prior myocardial infarction (12% versus 13%) and the frequency of multivessel coronary disease (55% versus 42%) were similar between the t-PA/streptokinase and the t-PA groups. There were no differences between the two groups in baseline heart rate, blood pressure, and the number of patients who experienced arrhythmias or hypotension before randomization. Time from symptom onset to initiation of drug therapy averaged 2.9 hours in the t-PA/streptokinase and 3.0 hours in the t-PA groups. Median times from drug administration to arteriography were 94 and 95 minutes in the combination and the monotherapy groups, respectively (\( p=NS \)).


**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>t-PA/SK (n=109)</th>
<th>t-PA (n=107)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>53±11</td>
<td>55±11</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Prior myocardial infarction (%)</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Anterior infarct location (%)</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>99±17</td>
<td>94±20</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129±26</td>
<td>130±21</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82±19</td>
<td>84±16</td>
</tr>
<tr>
<td>Time to treatment (hr)</td>
<td>2.9±1.2</td>
<td>3.0±1.2</td>
</tr>
<tr>
<td>Median time from drug to angiography (min)</td>
<td>94</td>
<td>95</td>
</tr>
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</table>

**Coronary Patency**

In 12 patients (seven t-PA/streptokinase and five t-PA), emergency angiograms were not obtained because of death (n=1), patient refusal (n=4), or inability to quickly transport the patient from a referral hospital (n=7). Thus, acute angiographic data were available in 102 patients for each group. Despite similarities in time to treatment and angiography, a patent infarct vessel was present in 79% (CI=0.71–0.87) of patients who received combination therapy compared with only 64% (CI=0.55–0.73) in patients who received conventional t-PA therapy (p<0.05) (Figure 2). In patients with failed thrombolysis, preparation for PTCA required obtaining venous access, exchanging arterial sheaths, and preparing balloon and guiding catheters. This generally required an additional 15–20 minutes. During the guiding shots before PTCA, additional vessels were noted to have reperfused, particularly in the t-PA arm. Therefore, in the absence of PTCA, 81% of vessels in the combination arm were ultimately patent compared with 71% of vessels in the full-dose t-PA arm (p=0.07). With addition of salvage PTCA in vessels that failed thrombolysis, acute patency rates were increased to 96% in both treatment groups.

Because streptokinase has been reported to be most effective in patients who are treated within the early hours of infarction, a subgroup analysis was performed based on time to treatment. Fifty-four percent of patients received thrombolytic therapy within the first 3 hours of symptom onset. In this early treatment subset, t-PA/streptokinase resulted in a 90-minute patency rate of 89% compared with 56% in the t-PA arm (p<0.0005). Patency rates were similar (67% and 73% after combination and t-PA therapy, respectively; p=0.51) in patients who were treated between 3 and 6 hours from symptom onset.

**Infarct Vessel Reclosure**

Follow-up angiograms were obtained in 85% of surviving patients, 89 of whom received t-PA/streptokinase and 86 received t-PA. Overall, infarct vessel reclosure was documented in three of 89 (3%) patients with follow-up catheterization in the combination arm (Figure 3). Nine of 86 (10%) patients in the full-dose t-PA arm were documented to have reclosure (p=0.06). Among patients with a patent

![Figure 2. Bar graph of acute coronary patency rates at the 90-minute angiogram, before and after PTCA. tPA, tissue-type plasminogen activator; SK, streptokinase; PTCA, percutaneous transluminal coronary angioplasty.](http://circ.ahajournals.org/Downloaded from http://circ.ahajournals.org/)

**FIGURE 2.** Bar graph of acute coronary patency rates at the 90-minute angiogram, before and after PTCA. tPA, tissue-type plasminogen activator; SK, streptokinase; PTCA, percutaneous transluminal coronary angioplasty.
vessel after thrombolytic therapy alone, reocclusion rates were 3% and 10% in combination and full-dose t-PA groups, respectively (p=0.07). In vessels requiring PTCA-mediated reperfusion after failed thrombolysis, reocclusion occurred in only one of 12 (8%) patients in the combination arm and three of 24 (13%) patients in the full-dose t-PA arm (p=0.71).

**Left Ventricular Function**

Technically adequate contrast left ventriculograms were available from the acute study in 174 patients (87 t-PA/streptokinase and 87 t-PA) and at follow-up in 148 patients (73 t-PA/streptokinase and 75 t-PA). As demonstrated in Table 2, despite similar ejection fractions at baseline ventriculography (52±12% versus 51±13%, p=0.78), the t-PA/streptokinase group tended to have a higher ejection fraction at follow-up (55±14%) than the t-PA group (51±12%, p=0.07). Likewise, baseline infarct zone function was similar between the two groups (−2.6±1.1 SD/chord versus −2.7±1.0 SD/chord, p=0.78); however, the t-PA/streptokinase group had superior infarct zone function at follow-up (−1.9±1.2 SD/chord) compared with the t-PA group (−2.3±1.2 SD/chord, p<0.05) (Figure 4).

Bedside radionuclide ventriculograms (n=175) obtained within 24 hours demonstrated similar ejection fractions between t-PA/streptokinase and t-PA groups (52±14% versus 50±13%, respectively; p=0.32). At follow-up, resting radionuclide ejection fractions (n=146) were not significantly different in t-PA/streptokinase compared with t-PA groups (52±13% versus 49±12%, p=0.14). However, the duration of supine bicycle exercise was significantly longer in the t-PA/streptokinase group (10.7±3.3 minutes) than in the t-PA group (9.1±3.1 minutes, p<0.005). Ejection fraction at peak exercise also tended to be greater in the t-PA/streptokinase group than in the t-PA group (59±15% versus 54±15%, p=0.06).

**Clinical Outcome**

In-hospital clinical events are outlined in Table 3. Recurrent unstable ischemia occurred in 10% of patients in the combination arm compared with 16%

### Table 2. Regional and Global Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>t-PA/SK</th>
<th>t-PA</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Contrast ejection fraction (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>174</td>
<td>52±12</td>
<td>51±13</td>
<td>0.78</td>
</tr>
<tr>
<td>Day 7</td>
<td>148</td>
<td>55±14</td>
<td>51±12</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Infarct zone (SD/chord)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>174</td>
<td>-2.6</td>
<td>-2.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Day 7</td>
<td>148</td>
<td>-1.9</td>
<td>-2.3</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Radionuclide ejection fraction (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest (day 1)</td>
<td>175</td>
<td>52±14</td>
<td>50±13</td>
<td>0.32</td>
</tr>
<tr>
<td>Rest (day 7)</td>
<td>146</td>
<td>52±13</td>
<td>49±12</td>
<td>0.14</td>
</tr>
<tr>
<td>Stress (day 7)</td>
<td>140</td>
<td>59±15</td>
<td>54±15</td>
<td>0.06</td>
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</table>

t-PA, tissue-type plasminogen activator; SK, streptokinase.
TABLE 3. In-Hospital Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>t-PA/SK (%)</th>
<th>t-PA (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ischemia</td>
<td>10</td>
<td>16</td>
<td>0.2</td>
</tr>
<tr>
<td>Reocclusion</td>
<td>3</td>
<td>10</td>
<td>0.06</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0</td>
<td>4</td>
<td>0.04</td>
</tr>
<tr>
<td>Emergency bypass</td>
<td>1</td>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* t-PA, tissue-type plasminogen activator; SK, streptokinase.

in the t-PA arm (p=0.2). Reinfarction (0% versus 3%, p=0.04) and the need for emergency bypass surgery for unstable ischemia (1% versus 6%, p=0.05) were reduced after combination therapy compared with full-dose t-PA.

Mortality rates were similar in the t-PA/streptokinase and t-PA groups, 6% versus 4%, respectively. The slightly greater mortality in the combination arm was attributed to inappropriate patient enrollment in two patients and a catheterization laboratory complication in one patient.

**Side Effects**

Thrombolytic drugs were prematurely discontinued in four patients: two patients with t-PA therapy who developed early bleeding complications, one patient with a presumed allergic reaction (rash) during t-PA/streptokinase therapy, and one patient with t-PA/streptokinase therapy who developed prolonged hypotension and cardiogenic shock. As demonstrated in Table 1, the frequency of hypotension before randomization, during drug infusion, and during catheterization did not differ between the two treatment groups. Furthermore, catheterization hemodynamics including heart rate, arterial pressure, and left ventricular end-diastolic pressure were similar in t-PA/streptokinase and t-PA alone groups.

Despite marked differences in plasma levels of fibrinogen (Figure 5), the prevalence and severity of bleeding complications were similar between the two treatment groups. As demonstrated in Table 4, hematoma or bleeding at the catheterization site was present in 49% of patients in the combination arm compared with 45% in the t-PA arm. One instance of retroperitoneal bleeding occurred after combination therapy. Hematuria and gastrointestinal bleeding were infrequent in both treatment groups. Stroke occurred in 2% of patients in each group, but was hemorrhagic in only one patient who was in the combination arm. This was a 65-year-old man with a long-standing history of hypertension and a stroke in the preceding year. He failed reperfusion, and during his salvage PTCA procedure, he received 18,000 units heparin and 250,000 units i.e. streptokinase (protocol deviation). Approximately 16 hours after thrombolytic therapy, he developed mental status changes, and right parietal bleeding was diagnosed. Of note, all four patients with strokes had nearly complete neurological recovery. Serious bleeding complications (defined as any intracranial, retroperitoneal, or gross gastrointestinal bleeding or the need for blood transfusion) were similar between the two groups (12% after combination therapy versus 11% after t-PA). Furthermore, the nadir hematocrit level, the number of patients who required a transfusion, and the average number of packed red blood cell units transfused were identical between the two groups.

**Discussion**

Many studies have demonstrated that infarct vessel patency13–16 and early treatment10,17 are important determinants of survival after thrombolytic therapy. Although several thrombolytic agents are now available, each has limitations when used individually. Combinations of thrombolytic drugs recently received attention because of several potential advantages: synergism, enhanced patency rates, reduced reocclusion, reduced bleeding complications, or reduced cost. The purpose of this study was to determine whether a combined regimen consisting of t-PA and streptokinase was equivalent or superior to conventional t-PA therapy in achieving and maintaining infarct vessel patency at a reduced expense. Because reocclusion may occur frequently within the first 24 hours,4–6 we chose to measure patency both acutely and before discharge. Ninety-minute patency was...
selected to allow our results to be easily compared with other acute patency studies.\textsuperscript{1–9} The major findings of this trial were that the combination of t-PA with streptokinase achieved a greater early patency rate and a trend toward reduced reocclusion. This rapid and sustained coronary patency after t-PA/streptokinase therapy resulted in better preservation of left ventricular function and exercise capacity. Because the relatively small sample size did not allow meaningful conclusions to be drawn about mortality rates, the present study was not designed to examine mortality as an end point.

**Acute Patency**

The combination of t-PA with streptokinase resulted in a 90-minute patency rate of 79%. These results are comparable to patency rates observed in other combination trials using 50 mg t-PA with streptokinase\textsuperscript{8,18} as well as trials using higher doses of t-PA (1 mg/kg) with urokinase.\textsuperscript{6,7} Streptokinase likely contributed to the high patency rate in the combination arm because the t-PA arm received higher doses of t-PA (70 mg) within the first 90 minutes and had a lower patency rate (64%). Whether a synergistic relation exists between t-PA and streptokinase is not known because dose-ranging studies of the combination have not been performed. Perhaps the systemic fibrinogenolysis or fibrin degradation products produced by streptokinase therapy may prevent the early intermittent reocclusion during t-PA infusion,\textsuperscript{19–21} thus resulting in a higher patency rate at 90 minutes.

The 90-minute patency rate observed after t-PA therapy (64%) is low but still within the 95% confidence intervals reported by other investigators.\textsuperscript{1,2,5,7,22–25} It has been reported that black race,\textsuperscript{26} normal hematocrit levels (43–47%), the use of immediate intravenous nitroglycerin,\textsuperscript{25} and intravenous heparin\textsuperscript{27,28} may enhance patency rates after t-PA therapy. Our patient population consisted of only 2% blacks and of only 33% patients who had a baseline hematocrit level between 43% and 47%. Furthermore, intravenous nitroglycerin was not routinely used, and heparin was not initiated until the time of cardiac catheterization. These factors may have influenced the patency rate after t-PA monotherapy in our study relative to other reports.

Although serial angiograms were not routinely performed, we observed that some additional arteries opened with t-PA during the time required to prepare for salvage PTCA. Therefore, in the absence of PTCA, differences in patency between t-PA/streptokinase and conventional t-PA therapy were no longer significant (81% versus 71%, \(p=0.07\)). Although t-PA/streptokinase may achieve patency more quickly, ultimate patency may be similar to t-PA monotherapy.

Considerable controversy exists regarding the optimal dosing regimen of t-PA. We chose to compare our investigational drug combination with the only dosing regimen of t-PA approved by the Food and Drug Administration. With conventional t-PA dosing, only 70 mg t-PA is infused within the first 90 minutes. Although the data are conflicting, “front-loaded” t-PA dosing regimens may achieve higher acute patency rates than that observed with the conventional dose of t-PA.\textsuperscript{29–31} Although Neuhaus et al\textsuperscript{29} reported that rapid infusion of t-PA resulted in a 90-minute patency rate of 90\%, these results were not confirmed by other investigators. Carney et al\textsuperscript{31} found that accelerated dosing of t-PA resulted in a greater patency rate at 60 minutes, but the 90-minute patency rate was similar to conventional t-PA dosing. Wall et al\textsuperscript{30} tested four different accelerated dosing regimens of t-PA and found patency rates ranging from 64\% to 83\%. Furthermore, there is concern that accelerated dosing of t-PA may increase the rate of serious bleeding complications. Early in the TIMI-2B study, with the administration of 150 mg t-PA during 6 hours (90 mg of which were given during the first hour), the rate of intracranial hemorrhage was 1.9\%. Therefore, we believed that our investigational combination thrombolytic regimen should be compared with the standard dose of t-PA.

**Reocclusion**

The combination of t-PA with streptokinase resulted in lower rates of reocclusion, reinfarction, and need for emergency bypass surgery for unstable ischemia compared with t-PA alone. The low rate of reocclusion after combinations of t-PA with either streptokinase or urokinase\textsuperscript{6–8,18} may be due to interference of fibrin polymerization\textsuperscript{32} and antiplatelet effects\textsuperscript{33,34} of fibrin degradation products or prolonged depletion of circulating fibrinogen that may allow time for healing of injured endothelium. A recent study demonstrated more thorough clot lysis with combination t-PA and urokinase than that achieved with either thrombolytic agent alone.\textsuperscript{7} Although all patients in our study received early aspirin and a 3,000–5,000-unit i.v. bolus of heparin, the heparin maintenance infusion was temporarily discontinued when serum fibrinogen levels were less than 100 mg/dl. Because most patients receiving t-PA/streptokinase did not receive continuous intravenous infusion of heparin during the first 24 hours, early heparin therapy may not be necessary after this combination regimen.

**Left Ventricular Function**

No significant differences in regional or global left ventricular function were observed between the two groups during acute studies. By the time of hospital discharge, however, patients who received t-PA/streptokinase had significantly better infarct zone function and a trend toward superior ejection fraction at rest and with exercise. Rapid and sustained coronary patency that was achieved with t-PA/streptokinase therapy is likely responsible for greater preservation of ventricular function. Others have suggested that streptokinase may have additional beneficial effects of reducing afterload,\textsuperscript{35} lowering
serum viscosity,36 and reducing reperfusion injury,37 which also may affect myocardial salvage.

Serum Fibrinogen Levels

Previous studies demonstrated that administration of 1.5 MU streptokinase alone was associated with a marked depletion in measured fibrinogen levels.38 It was not surprising that the combination of 50 mg t-PA with 1.5 MU streptokinase resulted in depletion of serum fibrinogen. Although preservation of circulating fibrinogen was thought to be a potential advantage in reducing bleeding complications, laboratory measures of the “lytic state” may not correlate well with bleeding complications38,39 Our data and others suggest that prolonged depletion of serum fibrinogen may be advantageous in reducing reocclusion.5–8,18,40

Bleeding Complications

Despite the marked differences in serum fibrinogen levels, bleeding complications were similar between t-PA/streptokinase and t-PA groups. Intracranial bleeding occurred in only one patient after t-PA/streptokinase therapy. Pooling data from this study and others8,18 suggests that the incidence of intracranial hemorrhage is 0.5% after t-PA/streptokinase therapy. The lack of increased bleeding in our trial and other combination trials6–8,38 may be related to the lower dose and short infusion duration of t-PA and avoiding intravenous heparin during the systemic fibrinolytic state.

Dosing of Thrombolytic Drugs

Although 1 mg/kg t-PA has been used in conjunction with urokinase in other trials,6,7 the 50-mg dose of t-PA was selected primarily to reduce thrombolytic drug costs because Activase is packaged in a 50-mg vial. It is unlikely that a higher dose of t-PA would achieve greater patency rates6,7 and may increase the risk of bleeding.35 Although a lower dose of t-PA might have further reduced bleeding complications, a study using 25 mg t-PA with urokinase resulted in low patency rates.6 The optimal dose infusion and duration of concomitant streptokinase therapy are also not known, and preliminary data suggest that combining 50 mg t-PA with 1 million units streptokinase may be adequate.18

Thrombolytic Costs

The pharmacy at the University of Kentucky is charged $87 for streptokinase. With the usual 40% markup, the charge to the patient for streptokinase therapy is $122. For a 100-mg dose of t-PA, our pharmacy is charged $2,300. With the 40% markup, this results in a cost of $3,220 to the patient. Our regimen of half-dose t-PA with streptokinase was effective, yet it resulted in a cost of only $1,230 to the pharmacy and $1,730 to the patient or nearly one half the cost of conventional t-PA therapy.

Given the international concern over cost containment in medicine, the expense of pharmaceutical agents remains an important issue. For example, at current prices, administration of t-PA or urokinase, or both, could consume half or more of the Medicare reimbursement for the diagnosis-related groups (DRG) category of uncomplicated myocardial infarction.41,42 Therefore, a regimen that can achieve maximal obtainable reperfusion at a cost reduction would be a great advantage. Relative to other reported thrombolytic strategies, these data indicate that our regimen may achieve a high rate of infarct vessel patency and a low incidence of reocclusion at a significant savings in pharmaceutical cost.

Limitations of the Study

The purpose of this study was to compare the combination of t-PA and streptokinase with conventional t-PA therapy. This does not address comparability of the combination to “front loaded” t-PA regimens. Whether the early patency rate would have been improved by accelerated dosing of t-PA monotherapy remains to be established. Furthermore, the frequency of serious bleeding complications such as intracranial hemorrhage cannot be accurately assessed because of the relatively small sample size.

Conclusions

This study has demonstrated that a combination of half-dose t-PA with streptokinase produced favorable results compared with conventional t-PA therapy in the rate of infarct vessel patency, reocclusion, and myocardial salvage. Because there was no additional bleeding tendency with this regimen, concomitant use of t-PA with streptokinase may provide a viable alternative to t-PA monotherapy at a substantial reduction in pharmaceutical cost.

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References


**KEY WORDS**  
*thrombolysis*  
*reperfusion*  
*myocardial infarction*  
*ventricular function*  
*streptokinase*  
*plasminogen activator, tissue-type*  
*combination thrombolytic therapy*
A prospective, randomized trial comparing combination half-dose tissue-type plasminogen activator and streptokinase with full-dose tissue-type plasminogen activator.

Kentucky Acute Myocardial Infarction Trial (KAMIT) Group.

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