A Randomized Controlled Trial of Intravenous Tissue Plasminogen Activator and Early Intravenous Heparin in Acute Myocardial Infarction

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To evaluate the coronary thrombolytic efficacy of tissue plasminogen activator (t-PA) and early intravenous heparin, 134 patients with acute myocardial infarction were randomly assigned to combination therapy or t-PA only. At a median of 2.78 hours from symptom onset, 64 patients received both t-PA (1.5 mg/kg/4 hr) and a bolus of 10,000 units heparin, whereas 70 patients received t-PA alone at the same dose. All patients underwent coronary angiography 90 minutes after initiation of therapy to determine infarct vessel patency status, after which time the control group patients were eligible to receive heparin. Baseline demographic and angiographic characteristics were similar for the groups. Infarct vessel patency was 50 of 63 (79%) for combination t-PA and heparin and 54 of 68 (79%) for t-PA alone. Bleeding complications, as reflected by need for transfusion, were similar in the two groups: 13% in the patients treated with t-PA and heparin compared with 18% in patients treated with t-PA only (p=0.53). The only intracranial hemorrhage in the trial occurred in a patient initially treated without heparin. Fibrinogen at 50 minutes after therapy was 32% decreased from baseline for the t-PA and heparin-treated patients compared with a 39% decrease in the control group. Predischarge left ventricular ejection fraction was similar for the two groups: 49.0±10.1% versus 50.2±11.9% for combined versus t-PA only therapy, respectively. We conclude that early intravenous heparin does not facilitate the fibrinolytic effect of t-PA at the doses tested. If given, heparin therapy can be deferred for at least 60–90 minutes after t-PA has been initiated. (Circulation 1989;79:281–286)

Recent experimental studies have demonstrated the facilitative interaction between heparin and tissue plasminogen activator (t-PA) for increasing fibrinolytic activity.1–3 In a canine model of peripheral artery thrombosis, Cercek et al1 observed 250% increased thrombolysis by combining t-PA and heparin compared with t-PA alone. The majority of clinical trials of intravenous t-PA have incorporated the use of early heparin.4–6 In one trial in which heparin was not given in the early period after t-PA, the early patency rate was 66%,7 representing a lower rate of infarct vessel patency when compared with other t-PA trials.8–11 These studies suggest that recanalization rates below 75–82% at 90 minutes after therapy should be regarded as suboptimal. Based on these results, a...
recent medical review reported that "the effectiveness of t-PA without heparin is unknown." Accordingly, we designed a randomized, controlled trial to evaluate the combination of t-PA with early intravenous heparin versus t-PA monotherapy.

**Methods**

**Patient Population**

Patients with an acute myocardial infarction less than 4 hours after symptom onset or less than 6 hours if severe ongoing chest discomfort was present were considered for entry into the study. Electrocardiographic ST segment elevation of 1 mm or more in two or more contiguous leads was required. Patients were excluded for age if 75 years of age or older; history of recent stroke, trauma, or surgery; bleeding predisposition; cardiogenic shock unresponsive to volume expansion; and previous Q wave infarction in the distribution of the infarct-related artery. Approval by the institutional review board was granted to each site before enrollment, which began on April 7, 1987, and ended on August 28, 1987.

**Protocol**

The protocol of the first clinical trial (TAMI-1) of the Thrombolysis and Angioplasty in Myocardial Infarction collaborative study group 4 and the second study (TAMI-2) 13 was used except for a change in the thrombolytic and anticoagulant regimen. After giving informed consent, patients were randomly assigned to receive either 10,000 units i.v. heparin bolus or no heparin. Within each participating clinical center, randomization was accomplished by a group of consecutively numbered sealed envelopes containing a treatment assignment generated at the biostatistical core laboratory. Concurrent to this, patients received 1.5 mg/kg t-PA i.v. (Genentech, South San Francisco, California) over 4 hours through a separate infusion line with normal saline. The dose was 1.0 mg/kg over the 1st hour, with 10% given as a bolus, and the maximum 1st hour dose of 90 mg. Over the next 3 hours, 0.5 mg/kg were given not to exceed a total maintenance infusion of 45 mg. After the infusion was begun, patients were transferred directly to the cardiac catheterization laboratory at one of four clinical sites. A single arteriogram of the infarct vessel was obtained 60 minutes after treatment when feasible. As close as possible to 90 minutes after treatment had been started but not before 90 minutes had passed, up to four injections into the infarct-related artery were given, and images were obtained in multiple angulated views. Infarct vessel patency was assessed after the fourth diagnostic angiogram with the Thrombolysis in Myocardial Infarction (TIMI) grading system. 4-5 After the determination of patency, patients not initially randomized to receive heparin were eligible to receive 5,000 units intravenously.

If the infarct vessel was patent (TIMI 2 or 3 flow pattern), no angioplasty was performed. For patients with persistent occlusion (TIMI 0 or 1 flow), "rescue" angioplasty 13 was performed after the final diagnostic angiogram. The angioplasty protocol has been previously described. 9,13 After leaving the catheterization laboratory, all patients were treated with the following medical regimen: 500–1,000 units i.v. heparin/hr, adjusted to keep the partial thromboplastin time at one and one half to two times the control level for at least 24 hours; 325 mg oral aspirin/day; and 30–60 mg oral diltiazem/6 hr. β-Blockers were not begun during the study period except to treat hypertension, recurrent angina, or arrhythmias.

**Angiographic Studies**

All cineangiographic films were forwarded to the angiographic core laboratory for blinded review by a single observer of each angiogram and ventriculogram. The infarct vessel patency was evaluated for TIMI grade (0–3). 4,5 and quantitation of the residual stenosis with the use of an automated edge detection computer algorithm. 14 End-systolic and end-diastolic left ventricular cavity outlines were digitized and stored in a digital radiographic computer (DPS, 4100C, ADAC Laboratories, Milpitas, California) for subsequent processing. Global ejection fraction was determined by the area-length method 15 and regional wall motion of the infarct zone by the centerline chord method. 16 Technically inadequate studies due to lack of opacification or frequent ventricular extrasystoles were not included in the analysis.

**Bleeding and Coagulation Variables**

Bleeding was categorized as previously described. 9,13 Major bleeding referred to intracranial hemorrhage or the requirement of transfusion of 2 or more units packed red blood cells. The bleeding site, baseline and nadir hematocrit, and units transfused were recorded for all patients. Blood samples collected on 0.01 M citrate and 200 kIU/ml aprotinin at baseline and 1, 4, and 24 hours after fibrinolytic therapy were immediately processed and kept frozen at -20°C until assayed in the hematology core laboratory. Fibrinogen was determined by a coagulation rate assay. 17 Fibrinogen degradation products were analyzed by the tanned red cell agglutination inhibition technique. 18

**Clinical Endpoints**

Reocclusion was defined by angiographic confirmation of TIMI 0 or 1 flow after previously documented TIMI 2 or 3 flow at the initial cardiac catheterization. Recurrent ischemia refers to 20 minutes or more of recurrent chest discomfort, accompanied by electrocardiographic ST segment changes, unresponsive to nitrate therapy, prompting urgent cardiac catheterization. A second rise in creatine kinase with positive myocardial isoenzyme fraction, accompanied by recurrent clinical signs, defined reinfarction. Emergency coronary bypass surgery denotes direct transfer from the cardiac catheteriza-
tion laboratory to the operating room for either failed angioplasty or high risk coronary anatomy.

Sample Size and Data Analysis

The primary endpoint for the trial was patency of the infarct-related artery at 90 minutes after therapy. Before the start of the study, it was determined that 132 patients (66 in each treatment group) would be required to demonstrate a 20% difference in patency between the two groups of randomized patients, assuming \( \alpha = 0.05 \), power = 0.80, and a patency rate of 67% or greater in the control group.

Values are expressed as mean ± SD unless otherwise specified. For discrete variables, group comparisons were made with the \( \chi^2 \) test. The Wilcoxon rank sum test was used for comparing groups with respect to continuous variables, and the Wilcoxon signed rank test was used for comparison of early to 7-day global and regional left ventricular function.

Case report forms were completed by the clinical research nurse coordinators and reviewed by the principal investigator at each site before submission to the Duke Data Coordinating Center. The data were verified independently by study monitors from review of the clinical records.

Results

The baseline demographic, angiographic, and hemodynamic characteristics of the patients are tabulated (Table 1). The number of patients on long-term aspirin or nonsteroidal anti-inflammatory agent treatment before entry were similar for the two groups. In the t-PA and heparin group, 23 patients were taking aspirin, and three patients were taking nonsteroidal anti-inflammatory agents; of the t-PA alone patients, 26 were taking aspirin and two were taking nonsteroidal anti-inflammatory agents. Except for an increase in multivessel disease among patients in the control group, there were no significant differences between the groups. Of note, coronary angiography was performed at a similar time from initiation of therapy for both groups.

At the initial angiogram, patency was demonstrated in 79% of patients receiving t-PA and heparin compared with 73% for t-PA alone \((p=0.41)\). After up to four contrast injections at the final diagnostic coronary angiogram of the infarct vessel, patency was 50 of 63 (79%) in the combination group patients and 54 of 68 (79%) in the patients treated with t-PA. The TIMI flow grades for the two groups were similar (Figure 1). Patency data for three patients (two in the t-PA group; one in the combination group) are not included because they lacked enzymatic confirmation of myocardial infarction and either had no significant atherosclerotic disease or had no definite infarct related artery.

For failure of thrombolytic therapy to achieve recanalization after 90 minutes, 21% of patients receiving t-PA and heparin compared with 17% of those assigned to t-PA only underwent rescue coronary angioplasty. The success rate of immediate angioplasty was similar: 10 of 13 (77%) compared with 11 of 12 (92%) for t-PA and heparin compared with control, respectively. Emergency bypass surgery was performed in 11% compared with 3% of patients for left main equivalent stenosis. Elective bypass surgery was performed before hospital discharge in three of 64 (5%) patients receiving the combination compared with 12 of 70 (17%) control patients, reflecting the higher frequency of multivessel disease in the latter group. Clinical outcomes are summarized in Table 2.

Bleeding complications were similar for the two groups. All occurred more than 90 minutes after

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>t-PA plus heparin</th>
<th>t-PA</th>
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</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td>Time to therapy (median, hr)</td>
<td>2.98</td>
<td>2.63</td>
</tr>
<tr>
<td>Age (median, yr)</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Infarct-related artery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
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<td>3</td>
</tr>
<tr>
<td>Number of diseased vessels†</td>
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<td></td>
</tr>
<tr>
<td>One or none</td>
<td>45%</td>
<td>39%*</td>
</tr>
<tr>
<td>Two</td>
<td>42%</td>
<td>30%</td>
</tr>
<tr>
<td>Three</td>
<td>13%</td>
<td>31%</td>
</tr>
<tr>
<td>Time to angiography (median, min)</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Systolic blood pressure (median, mm Hg)</td>
<td>126</td>
<td>130</td>
</tr>
<tr>
<td>Heart rate (median, beats/min)</td>
<td>76</td>
<td>76</td>
</tr>
</tbody>
</table>

*With the exception of number of diseased vessels \((p=0.03)\), there were no significant differences \((p>0.05)\) in baseline characteristics for the two groups.

†50% or greater stenosis of a major epicardial coronary artery.

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**Figure 1. Bar graph of infarct-related artery recanalization at 90 minutes of therapy by TIMI Grade⁴ for tissue plasminogen activator (t-PA) and heparin (n=64) vs. t-PA alone (n=70) patients. No differences between the groups were observed.**
initiation of t-PA. The requirement for transfusion for patients not undergoing bypass surgery was seven of 53 (13%) in the t-PA and heparin patients compared with nine of 51 (8%) in the control group ($p=0.53$). The only intracranial hemorrhage occurred in a patient who received t-PA but not heparin at the initiation of therapy. This patient is a 54-year-old man with no history of hypertension or cerebrovascular disease; he completely recovered from a left-sided parietal-occipital hemorrhage except for a slight expressive aphasia.

Fibrinogen at baseline was 2.7±0.9 and 2.8±1.2 g/dl in the heparin and control groups, respectively. After 50 minutes of therapy, the fibrinogen was 1.8±0.6 and 1.7±1.0, representing a 32% compared with 39% reduction from baseline, respectively ($p=0.57$).

Global and regional left ventricular function data are shown in Figures 2 and 3. At baseline, mean ejection fraction was 49.9% and 49.1%, respectively, for patients with paired, technically adequate studies. At 7 days, there was no improvement for ejection fraction in either group (49.0% and 50.2%, respectively). The infarct zone wall motion was −2.56 and −2.48 SD/chord at baseline. At follow-up, there was improvement for both groups, with the change being significant only in the control patients (7-day value: −2.31 and −1.97 SD/chord, respectively). The trend for more recovery of infarct zone function among control group patients was not statistically significant ($p=0.19$).

Quantitative angiography of the infarct-related artery demonstrated a similar absolute diameter for patients treated with t-PA and heparin compared with t-PA alone (0.88 compared with 0.81 mm diameter for 62 and 56 evaluable patients, respectively; $p=0.57$) and little difference for percent diameter stenosis (71.6±15.2 compared with 74.2±13.2, respectively; $p=0.46$). The predischarge status of the infarct vessel is summarized in Table 3. After analysis of the data of 134 patients enrolled, an additional 30 patients were randomly assigned in this trial. There were no differences in the results for patency or other endpoints with the addition of the latter group to the initial series. The overall patency rate for t-PA and heparin combined was 65 of 81 (80%) compared with 65 of 80 (81%) in patients receiving t-PA alone ($p=0.87$). Having observed identical patency rates in the 134 patients, we determined that even if there existed a difference as large as 5% in coronary thrombotic efficacy between t-PA and heparin versus t-PA alone, at least 1,400 patients would be required in each treatment group, and this number is greatly increased if smaller differences were to be detected.

**Discussion**

The major finding of this trial was that the addition of early, high-dose intravenous heparin to tissue plasminogen activator did not significantly affect early coronary patency rates. Of note, no increase in early fibrinogen breakdown was observed with combination therapy, which supports the lack of a catalytic effect on the hemostatic system with concomitant heparin therapy. There was no incremental recovery or preservation of left ventricular function, and no differences in the clinical outcomes were observed, including bleeding.
Previous experimental studies have suggested a potentially important interaction between heparin and t-PA. Cercek and colleagues showed that lysis of canine femoral artery thrombosis was markedly increased by this combination compared with either agent alone. Andrade-Gordon and Strickland incubated t-PA and heparin in vitro and observed marked temporal activation of plasminogen with the combination when compared with t-PA alone. In a canine experimental model of coronary thrombolysis, Mckelson and coworkers showed that t-PA interacted favorably with heparin yielding more frequent and complete reperfusion and that this combination was more effective than one of streptokinase with heparin. Nearly all clinical trials using t-PA performed to date have incorporated early intravenous heparin in an attempt to avoid rethrombosis or reocclusion. The manufacturer for t-PA has recommended administration of 5,000 units heparin at the time when fibrinolytic therapy is initiated.

Although early intravenous heparin has frequently been jointly given with thrombolytic therapy on an empirical basis, there are no data from prospective clinical trials to support its use. The use of heparin as an anticoagulant poses an independent, significant risk of bleeding complications when used alone, and it remains possible that heparin and thrombolytic therapy may be additive for inducing hemorrhagic episodes. The major drawback of thrombolytic therapy is the potential for serious bleeding, and, in particular, the intracranial site is of foremost concern. If adjunctive heparin could be deferred in time or even eliminated from fibrinolytic therapy protocols, one would anticipate a reduced liability for such complications. The present study supports the lack of need for heparin during at least the first 90 minutes of t-PA treatment, when both the highest proportion of the cumulative dose is given and the maximum plasma levels are achieved.

Previous in vitro studies have demonstrated heparin competition with fibrin for binding of t-PA, resulting in increased activation of free plasminogen, reduced fibrin specificity, and less efficient thrombolysis. In contrast, Fry and Sobel have recently shown heparin’s lack of interference with binding of t-PA to thrombi in vitro at therapeutic concentrations. In the present study, the lack of effect of the heparin and t-PA combined therapy on fibrinogen depletion in vivo appears to confirm and extend this finding.

Clearly, there are some limitations of the current study. First, without a coronary angiogram before therapy, it was not possible to determine whether the addition of heparin increased the velocity of infarct vessel recanalization. However, the initial angiographic results were similar for heparin and control groups. Second, there is not adequate power in the trial to conclude that heparin and t-PA do not interact favorably to achieve more extensive or frequent coronary thrombolysis or in a negative fashion to induce a higher rate of bleeding complications. Based on the results of the present study, a trial of several thousand patients would be required to avoid a high type II error probability in making a definitive conclusion as to the lack of any t-PA and heparin interaction. Third, our observations and conclusions must be limited to the doses of t-PA and heparin used. It remains a possibility that with lower or subtherapeutic doses of t-PA, a potentiating influence of heparin might yet be demonstrated. However, such a clinical study is unlikely to be carried out because lower doses of t-PA, even in combination with early heparin and additional thrombolytic agents, yield suboptimal rates of infarct vessel patency. Such data in aggregate make the likelihood of the existence of a clinically significant heparin–t-PA synergistic effect a low probability.

In conclusion, the addition of early intravenous heparin to t-PA did not have any salutary clinical, angiographic, ventriculographic, or biochemical effect. Based on this study, it appears prudent to withhold heparin for at least the first 90–120 minutes of t-PA therapy to avoid the unnecessary hazard of bleeding complications. In light of our findings and others that point toward the lack of ability for heparin to inhibit reocclusion or recurrent ischemic events after t-PA, future clinical trials will be required to determine whether anticoagulation is necessary at any time as an adjunct to this form of fibrinolytic therapy.

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