Effect of Heparin on Coronary Arterial Patency After Thrombolysis with Tissue Plasminogen Activator in Acute Myocardial Infarction

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Infarct artery patency rates at 90 minutes after coronary thrombolysis using recombinant tissue-type plasminogen activator (rt-PA) with and without concurrent heparin anticoagulation have been shown to be comparable. The contribution of heparin to efficacy and safety after thrombolysis with rt-PA is unknown. In this pilot study, 84 patients were treated within 6 hours of onset of acute myocardial infarction (mean of 2.7 hours) with the standard dose of 100 mg of rt-PA over 3 hours. Forty-two patients were randomized to receive additionally immediate intravenous heparin anticoagulation (5,000 U of intravenous bolus followed by 1,000 U/hour titrated to a partial thromboplastin time of 1.5 to 2.0 times control) while 42 patients received rt-PA alone. Coronary angiography performed on day 3 (48 to 72 hours, mean 57) after rt-PA therapy revealed infarct artery patency rates of 71 and 43% in anticoagulated and control patients, respectively ($p = 0.015$). Recurrent ischemia or infarction, or both, occurred in 3 (7.1%) anticoagulated patients and 5 (11.9%) control patients (difference not significant). Mild, moderate and severe bleeding occurred in 52, 10 and 2% of the group receiving anticoagulation, respectively, and 34, 2 and 0% of patients in the control group, respectively ($p = 0.006$).

These data indicate that after rt-PA therapy of acute myocardial infarction, heparin therapy is associated with substantially higher coronary patency rates 3 days after thrombolysis but is accompanied by an increased incidence of minor bleeding complications.

(Am J Cardiol 1990;66:1412–1417)

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Anticoagulation has long played a role in the prevention and management of thromboembolic complications of acute myocardial infarction.[1-3] The role of antithrombotic therapy after pharmacologic thrombolysis in myocardial infarction is incompletely characterized. To date, in most trials, heparin anticoagulation has been routinely, but empirically, added to thrombolytic therapy of acute myocardial infarction in an effort to maximize thrombolytic efficacy and minimize the risk of thrombotic reocclusion.[3-5] The timing and dose of heparin have varied widely but it has been added to recombinant tissue-type plasminogen activator (rt-PA), streptokinase, anistreplase, urokinase and prourokinase (single chain urokinase-type plasminogen activator or scu-PA) in the setting of acute myocardial infarction.[6-13]

The contribution of heparin therapy to early coronary thrombolytic efficacy with rt-PA has been prospectively evaluated in a trial by the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group of 134 patients.[14] Infarct coronary arterial status was determined angiographically after 90 minutes in patients randomized either to rt-PA therapy alone or to rt-PA plus heparin (10,000 U intravenous bolus) delivered at the start of the rt-PA infusion. Coronary patency rates at 90 minutes were 79% in both groups. Thus, because anticoagulation did not play a significant role in achieving reperfusion, any expected effect of heparin would be observed after thrombolysis. However, in this trial all patients received heparin during and after angiography at 90 minutes, so the effects of anticoagulation on reocclusion, recurrent clinical events and bleeding after thrombolytic therapy could not be assessed. This pilot study assesses the role of heparin therapy after thrombolytic therapy of acute myocardial infarction with rt-PA.

METHODS

Patients: Patients experiencing acute myocardial infarction and presenting to one of the participating investigation sites were eligible for inclusion in this study. Myocardial infarction was defined as (1) chest pain of ≥30 minutes' duration and (clinically) consistent with coronary ischemia; (2) ST-segment elevation on electrocardiogram of ≥0.1 mV in at least 1 of 3 locations (anterior [≥2 of the 6 precordial leads V_1-V_6]; inferior [≥2 of 3 inferior leads (II, III, aVF)]; or lateral [leads I and aVL]); and (3) onset of index symptoms must have oc-

curred within 6 hours of the time of entry into the study protocol. Men and postmenopausal women were eligible for inclusion. Standard exclusion criteria for thrombolytic therapy in acute myocardial infarction were used.[6,7,9,10] Recent therapy with aspirin or other platelet inhibitory agent was not an exclusion criterion.

Protocol for study drug administration: After obtaining informed consent, all eligible patients received lidocaine therapy before and during thrombolytic therapy. Patients received 100 mg of alteplase, recombinant brand of t-PA (Activase®), provided by Genentech, Inc. of South San Francisco. Administration was initiated with a bolus of 6 mg given intravenously over 2 minutes followed by 54 mg infused over the first hour. The remaining 40 mg was delivered at 20 mg/hour during the second and third hour of the infusion.

Each center was provided with a treatment allocation sequence based on a randomly generated list of numbers. In patients randomized to receive anticoagulation, unblinded heparin therapy was initiated within the first hour of the rt-PA infusion with an intravenous bolus of 5,000 U followed with an infusion of 1,000 U/hour titrated to maintain the partial thromboplastin time at 1.5 to 2.0 times control value. The first partial thromboplastin time was determined 12 hours after initiation of the heparin infusion. Heparin was continued until the time of coronary angiography.

Patients entered into either arm of the study were precluded from receiving aspirin or dipyridamole during the study period.

Study end points: Because heparin has no angiographically observable effect during thrombolytic reperfusion,[14] the purpose of this study was to evaluate the role of heparin after rt-PA in the maintenance of infarct artery patency early during the course of acute myocardial infarction. The primary end point was coronary arterial patency rate documented on angiography performed on day 3 (48 to 72 hours) after therapy. Since patency rates at 90 minutes are similar in the presence or absence of heparin, any observed angiographic difference could be attributed to heparin effect. In addition, clinical reocclusion was defined by recurrence of (1) cardiac-type chest pain similar to that which occurred with the index myocardial infarction lasting ≥20 minutes, unrelieved by nitroglycerin; (2) electrocardiographic changes consistent with ischemia (described previously) in the same distribution as the index myocardial infarction; or (3) deterioration in clinical condition consistent with reinfarction. Electrical and mechanical complications were not considered study end points unless associated with reinfarction. Treatment of recurrent coronary ischemia and complications of infarction were at the discretion of the investigators.

The secondary end point of the study was evaluation of the contribution of heparin to the incidences of bleeding after thrombolytic therapy. All bleeding occurrences were noted, with recording of date, site and an estimate of severity according to the following classification: (1) minor—of no clinical consequence, not requiring transfusion, blood loss of <250 ml; (2) moderate—250 to 500 ml observed blood loss; (3) severe—>500 ml blood loss requiring transfusion for augmentation of hematocrit; and (4) life-threatening—evidence of any intracranial bleeding, or gastrointestinal or other internal bleeding causing hypotension. In cases in which >1 bleeding event was noted, the most severe instance was used for statistical analysis.

TABLE I Patient Population

	Group A—Anticoagulation	Group B—Control
Therapy	rt-PA plus heparin	rt-PA alone
No. of patients	42	42
Men (%)	79	83
Age (mean years)	59.4	56.6
Weight (mean kg)	80.3	81.4
Time from onset of chest pain to rt-PA therapy (mean hours)	2.6	2.8
Infarct location (%)		
Anterior (±lateral)	45	50
Inferior	55	50
Time from rt-PA therapy to angiography (mean hours)	59.6	55.1

p = not significant for all variables.
rt-PA = recombinant tissue-type plasminogen activator.

Protocol for angiographic studies: Coronary angiography was planned for all study patients 48 to 72 hours after treatment with thrombolytic therapy. Institutional protocol was followed during the angiographic procedure. Status of the infarct artery was determined during consensus reading by 2 senior angiographers according to Thrombolysis in Myocardial Infarction (TIMI) flow grade criteria.[15] Infarct arteries with TIMI flow grades 0 and 1 were further classified as "occluded" and flow grades 2 and 3 as "patent."

Statistical analysis: The purpose of this study was to estimate the magnitude of the heparin effect on the primary and secondary end points being evaluated (i.e., coronary arterial patency and bleeding complications, respectively). An initial total sample size of 100 patients was projected for this pilot effort. Fisher's exact test was used to determine significance of dichotomous variables and an exact test was used for ordered categorical variables.[16] All p values reported are 2-sided.

RESULTS

From October 1987 to August 1988, a total of 95 patients were randomized in this pilot clinical trial at 4 participating centers. For reasons described later, 11 patients did not undergo protocol angiography and are not included in the data analysis. Of 84 evaluable patients, 42 received rt-PA plus immediate heparin therapy (group A—anticoagulation) and 42 received rt-PA alone (group B—control). The baseline demographic and clinical characteristics of the 2 groups are listed in Table I.

Angiography was performed a mean of 59.6 hours after rt-PA treatment in the anticoagulation group and 55.1 hours after rt-PA in the control group. Infarct artery assessment revealed a significant difference in patency between the 2 groups. A TIMI flow grade of 2 or 3 was seen in 30 of 42 patients (71%) in the heparin group and in 18 of 42 patients (43%) in the control

TABLE II Sites of Bleeding Complications

	Anticoagulation	Control
Minor bleeding		
Venipuncture site	10	6
Ecchymosis	8	4
Upper extremity hematoma	4	3
Gingival bleeding	3	1
Microscopic hematuria	1	2
Occult gastrointestinal bleeding	1	2
Ear	1	0
Femoral hematoma	1	0
Skin due to trauma	1	0
Epistaxis	0	1
Tongue	0	1
Moderate bleeding		
Deltoid hematoma	1	0
Foot due to trauma	1	0
Hip hematoma	1	0
Knee effusion	1	0
Vaginal	0	1
Severe bleeding		
Oropharyngeal due to endotracheal trauma	1	0

Note: More than 1 bleeding complication occurred in some patients.

group (p = 0.015). One of the patients demonstrating clinical reocclusion in the control group died before angiography because of infarct extension and was considered to have an occluded infarct artery (grade 0). The results of angiography are illustrated in Figure 1.

Three patients (7.1%) in the group receiving heparin and 5 patients (11.9%) in the control group demonstrated protocol-defined clinical evidence of reocclusion during the study period. This difference did not approach statistical significance (p = 0.71). The mean time of reocclusion was similar in the 2 groups, 27.5 hours (range 5.3 to 71.0) in the heparin group and 28.4 hours (range 3.3 to 62.9) in the control group.

Bleeding occurred in 64% of patients in the group receiving heparin (minor bleeding in 52%, moderate in 10% and severe in 2%) and in 36% of patients in the control group (minor in 33% and moderate in 2%) (p = 0.006). Sites of bleeding are listed in Table II.

Eleven patients were excluded from the final analysis for the following reasons: Four patients died because of complications of the index myocardial infarction (not related to reinfarction) before undergoing angiography (2 from group A [sudden cardiac death in 1 and progressive cardiogenic shock in the other] and 2 from group B [sudden cardiac death in both]); in 2 patients, cardiac enzymes failed to confirm presence of myocardial infarction (1 each from groups A and B); 2 patients randomized to the control group received heparin owing to clinical considerations (1 for angiographically apparent intracoronary thrombus during angioplasty for failed thrombolysis and 1 as empiric therapy of recurrent chest pain not meeting above protocol criteria for reocclusion); and 1 patient in the control group was removed from the study because of physician preference (patient considered to be at "high risk" for continuation in the study; patient had neither bleeding complications nor recurrent ischemic complications). In addition, since the purpose of the study was to evaluate the postthrombolysis course, 2 patients experiencing complications during the rt-PA infusion were excluded from the final analysis: 1 patient experienced an autopsy-proven thromboembolic cerebrovascular accident during rt-PA therapy and 1 patient with an undisclosed history of recent motor vehicle trauma died during rt-PA therapy because of massive internal hemorrhage.

DISCUSSION

Patent artery hypothesis: The potential importance of a patent infarct artery during the recovery phase of acute myocardial infarction has recently been reviewed[17] and is the subject of ongoing clinical trials. Reduction in mortality and improved prognosis have been observed even when infarct artery reperfusion is presumed to have occurred as late as 24 hours after myo-

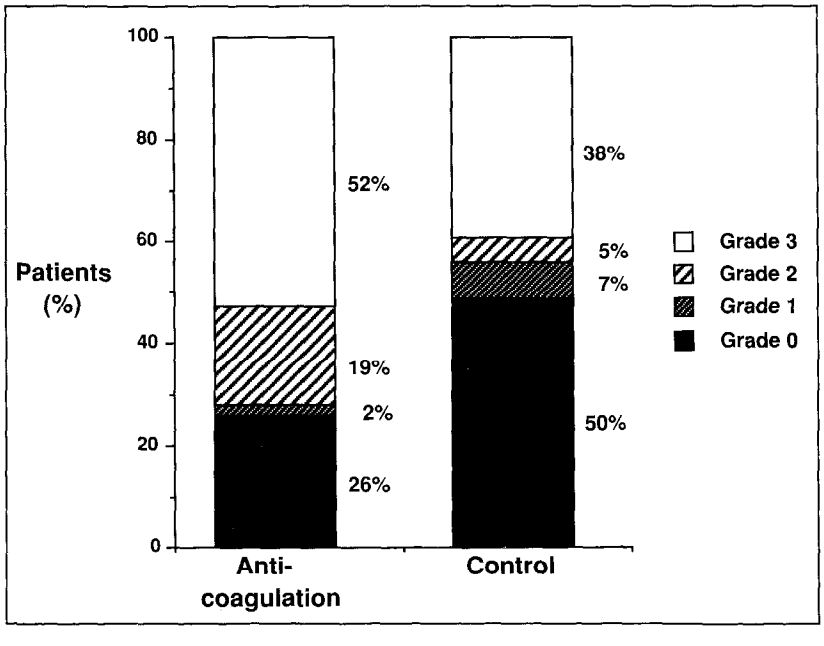

FIGURE 1. Results of angiography. Percentage of patients demonstrating angiographic Thrombolysis in Myocardial Infarction trial flow grades 0 to 3 are shown.

TABLE III Effect of Heparin Therapy on Mortality in ISIS-2 (18)

	Vascular Deaths/Number of Patients (% dead)		
	Streptokinase ± Aspirin	Streptokinase + Aspirin	Streptokinase Only*
Heparin therapy "planned" at entry			
Intravenous heparin	170/2,054 (8.3%)	66/1,024 (6.4%)	104/1,039 (10.2%)
Subcutaneous heparin	325/3,601 (9.0%)	137/1,805 (7.6%)	188/1,796 (10.4%)
No heparin	296/2,937 (10.1%)	140/1,463 (9.6%)	156/1,474 (10.6%)

Note: This was a prespecified subsidiary analysis of the trial.
* Calculated from published data, i.e., first 2 columns of table.

cardial infarction onset.[18-20] A corollary conclusion is that preservation of the benefits of early reperfusion depends on prevention of rethrombosis and reocclusion. Symptomatic reocclusion leading to recurrent ischemia and infarction represents the clinically apparent result of failure to maintain arterial patency. However, silent reocclusion has been documented[7,15] and may result in less readily apparent adverse clinical sequelae, e.g., silent ischemia.

After successful pharmacologic thrombolysis, residual clot and the disrupted endothelium represent potent thrombogenic stimuli that continue to activate the coagulation system.[2-5] The time course of the resolution of this risk is unknown. Empiric pharmacologic approaches to this situation have utilized a low-dose, continuous infusion of a thrombolytic agent, as well as the anticoagulant, heparin, which potentiates the efficiency of antithrombin III, the physiologic inhibitor of thrombin. Results of early trials evaluating the former approach after thrombolysis with rt-PA provided contradictory results: One study indicated that rethrombosis was a significant problem, especially in patients with high-grade residual stenosis, but could be prevented by several hours of a low-dose, continuous, "maintenance" infusion of rt-PA.[21] In contrast, a randomized study indicated that the rethrombosis rate was low and was similar in patients receiving, compared with those not receiving, a maintenance infusion.[22]

Despite these results, the most widely studied and currently recommended rt-PA regimens have included a 2- to 4-hour maintenance infusion aimed at reducing the rethrombosis rate.[6,7,23,24] In addition, as with other thrombolytic agents, heparin anticoagulation is recommended[6,12,23,25-29] though the optimal dose, duration and route of administration has not been extensively evaluated. Alternatively, rt-PA has been combined with non-fibrin-selective thrombolytic agents resulting in systemic fibrinogenolysis.[12,30,31] In these cases, the risk of rethrombosis due to persistent thrombin activity is theoretically reduced by removal of thrombin substrate, i.e., fibrinogen, with generation of fibrinogen degradation products. It has recently been shown that the risk of rethrombosis is inversely correlated with the levels of fibrinogen degradation products which act as potent anticoagulants.[32]

Thrombolysis with streptokinase and the role of heparin therapy: Information on the impact of heparin therapy is available from 6 trials of streptokinase in acute myocardial infarction.[18,33-37] The major ones include the Subcutaneous Calcium-Heparin in Acute Myocardial Infarction trial, a randomized multicenter study that compared 218 patients receiving streptokinase and intravenous/subcutaneous heparin (2,000 U intravenously at the time of enrollment followed by 12,500 U subcutaneously every 12 hours beginning 9 hours later) with 215 patients treated with streptokinase alone.[33] In-hospital mortality in the group receiving heparin was 4.5% compared with 8.8% in the control group ($p = 0.05$). Recurrent ischemia and reinfarction rates were reduced in the heparin group, but the differences did not reach statistical significance.

In the pilot study for the Second International Studies of Infarct Survival (ISIS-2), 619 patients were randomized in a $2 \times 2 \times 2$ factorial design to streptokinase or placebo, aspirin or placebo and heparin or placebo.[34] In this study, heparin was associated with a decrease in reinfarction from 4.9 to 2.2% (difference not significant) but no difference in mortality was observed.

The largest study from which information on heparin therapy is available is ISIS-2.[18] Even though it was designed primarily to evaluate the effects of streptokinase and aspirin on mortality after acute myocardial infarction, the study provides information on the outcome of patients receiving intravenous, subcutaneous or no heparin therapy. In all patients randomized to streptokinase and aspirin, mortality at 5 weeks was highest in patients receiving no heparin (9.6%), lower in those receiving subcutaneous heparin (7.6%) and lowest in those receiving intravenous heparin (6.4%) (Table III). Interestingly, the beneficial effect of heparin was limited to patients receiving aspirin in addition to streptokinase, whereas the beneficial effect of aspirin observed in this study was much greater in patients receiving heparin after streptokinase than in those not receiving heparin (Table III). This suggests an interaction between heparin and aspirin after thrombolysis with streptokinase.

Though not conclusive, these data suggest that anticoagulation with heparin may lead to increased bleeding but also may play an important contributory role in the reduction of mortality seen after streptokinase therapy. It appears that intravenous heparin is more effective than subcutaneous heparin, but that subcutaneous heparin may also exert a positive effect after streptokinase therapy. In light of the evidence supporting the impor-

tance of a patent infarct artery during recovery from acute myocardial infarction, it is probable that heparin exerts this effect through reduction in the incidence of rethrombosis and reocclusion, whether silent or clinically apparent, or through acceleration of the spontaneous thrombolysis that occurs after acute myocardial infarction.[38,39] If aspirin exerts beneficial effects through longer term prevention of reocclusion, more pronounced effects would be expected in patients with infarct artery patency initially maintained by heparin.

Thrombolysis with recombinant tissue-type plasminogen activator and heparin therapy: Sufficient data to evaluate fully the role of heparin (or aspirin) on the outcome of patients with acute myocardial infarction after treatment with rt-PA are not available. In the current study, although aspirin therapy was precluded after patient enrollment, a limitation of the protocol was that aspirin use before enrollment was not controlled. The potential impact of prior aspirin use on the observed results is unknown.

A recent study in Australia treated patients with acute myocardial infarction with 100 mg of rt-PA over 3 hours and intravenous heparin for 24 hours and then they were randomized to either continuation of intravenous heparin in 99 patients or conversion to aspirin and dipyridamole in 103 patients until coronary angiography was performed at 1 week.[40] The investigators concluded that anticoagulant therapy with intravenous heparin could be effectively and safely replaced with antiplatelet therapy as early as 24 hours after rt-PA. A small, randomized study also suggested that in many patients, after 24 hours, heparin does not protect against rethrombosis and does contribute to bleeding.[41]

Another study, the Heparin-Aspirin Reperfusion Trial (HART) was recently completed in over 200 patients comparing rt-PA plus heparin with rt-PA plus aspirin.[42] Utilizing angiography performed early (7 to 24 hours) and late (7 to 10 days), their preliminary data support an important early role for heparin anticoagulation in preserving infarct coronary patency after rt-PA therapy of acute myocardial infarction. In addition, this study confirms the relative effectiveness of aspirin in maintaining coronary patency during the period beginning 24 hours after thrombolysis and ending at 1 week.

Although not conclusive, the data on anticoagulation after thrombolysis with rt-PA and streptokinase suggest that the role of antithrombin therapy with heparin may be even more necessary to a favorable clinical outcome with rt-PA than with streptokinase because of 2 important pharmacologic factors: half-life and fibrin-selectivity. The elimination half-life of rt-PA is on the order of 5 minutes, while that of streptokinase is about 25 minutes. After the termination of the infusion, rt-PA is cleared from the blood within 30 minutes, while streptokinase circulates for several hours. If the importance of anticoagulation after rt-PA therapy is confirmed, the half-life of rt-PA may dictate the optimal time for initiation of such therapy. Fibrinogen degradation products are potent anticoagulants that are produced by the action of plasmin on fibrinogen.[32] The concentration of degradation products produced after therapy with the non–fibrin-selective agent streptokinase is over 2.5 times higher than that after the relatively fibrin-selective agent rt-PA, leading to a more pronounced and a more extended anticoagulant effect.[43]

Implications of current study: The current study suggests that heparin anticoagulation preserves coronary arterial patency after successful thrombolysis with rt-PA while modestly increasing the risk of minor bleeding complications after acute myocardial infarction. The magnitude of the difference observed in arterial patency rates (71 and 44%) was not reflected by a comparable difference in the incidence of clinical reocclusion (7.1 and 11.9%). This may have been due to the fact that this pilot study lacked the statistical power to detect this difference.

Alternatively, these results may reflect the physiologic implications of a patent infarct artery during the acute compared to the the recovery phase of acute myocardial infarction. During the initial phase of acute myocardial infarction, symptomatic ischemia and necrosis occur because of the imbalance between increased myocardial oxygen demand and decreased coronary blood flow. Successful thrombolysis acutely restores blood flow to a level sufficient to interrupt the ischemic process. Hours or days later, with myocardial oxygen demand returned to baseline levels because of normalization of heart rate and blood pressure, a reduction in coronary blood flow due to rethrombosis may not reproduce an oxygen supply-demand imbalance sufficient to cause recurrent symptoms in all cases. Recruitment of collateral circulation to the jeopardized zone may also play a protective role.[19]

The findings of the TAMI heparin trial combined with the results of this study and the preliminary report of the HART study imply that subacutely (i.e., up to 24 hours), after thrombolytic therapy with rt-PA, in the absence of adequate heparin anticoagulation, silent reocclusion may occur in a significant number of patients. The National Heart Foundation and HART studies further suggest that after 24 hours the need for aggressive anticoagulation diminishes. Since the large majority of infarct arteries are patent 10 to 14 days after myocardial infarction whether or not thrombolytic therapy has been administered, the so-called "catch-up" phenomenon,[17,39] such reocclusion may be transient and may be associated with initially subclinical sequelae, e.g., silent ischemia. Other studies are required to confirm the findings of this pilot study, to evaluate more fully the prognostic significance of silent reocclusion and to determine the adequate dose, timing and method of anticoagulation after thrombolysis with rt-PA.

Acknowledgment: We wish to acknowledge the assistance of Debra Brinkman, MSN, Jeri Faset, RN, Sherry Kerner Slemons, RN, Ruth Gieble, RN, and Janice Rolli-Mills, RNC.

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