A Randomized Pilot Trial of Brief Versus Prolonged Heparin After Successful Reperfusion in Acute Myocardial Infarction

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Controversy exists as to whether and how long heparin treatment is necessary after infarct vessel recanalization. To determine the role of heparin, patients with suitable angiographic features after reperfusion therapy were randomly allocated to receive a brief infusion of intravenous heparin for ≤24 hours (group 1), adjusted to a partial thromboplastin time of 2 times control or a prolonged infusion for ≥72 hours (group 2), using the same titration mechanism. Patients were excluded for complex intimal dissections, large residual filling defects, less than Thrombolysis in Myocardial Infarction grade 3 flow pattern or >50% residual stenosis. Heparin was sustained except for discontinuation 2 to 4 hours before periaccess sheath removal, or if significant bleeding (≥2 units blood transfusion) occurred. The primary endpoints were 1-week patency determined by repeat catheterization or recurrent ischemia, or both, and the incidence of bleeding complications. Fifty patients were randomized, 25 in both groups. Baseline variables were similar; 14 group 1 and 15 group 2 patients received thrombolytic treatment; 20 patients in each group had coronary angioplasty. Two documented reocclusions occurred in both groups. Significant bleeding complications occurred in 0 of 25 (0%) group 1 versus 6 of 25 (24%) group 2 patients ($p < 0.05$). Thus, in low-risk patients after successful reperfusion, prolonged heparin therapy does not protect against rethrombosis and is associated with a significantly higher rate of bleeding complications. Therefore, prolonged heparin therapy for >24 hours does not appear to be justified in low-risk patients with successful reperfusion.

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The treatment of patients after successful reperfusion therapy in the setting of an acute myocardial infarction is unclear. In most of the major trials evaluating reperfusion therapy,[1–3] the use of intravenous heparin has been empiric because of previous anecdotal reports suggesting that the level of anticoagulation was inversely related to the frequency of recurrent ischemic events.[4,5] There have been no randomized studies analyzing whether a prolonged infusion of heparin is beneficial in maintaining infarct-related artery patency in patients after successful reperfusion therapy. As previous studies have noted that a significant risk is associated with heparin treatment in patients with underlying medical problems,[6–8] we undertook this pilot trial to determine whether the risk of heparin therapy outweighed the benefit in a group of patients felt to be at low risk of reocclusion after successful reperfusion in the setting of acute myocardial infarction.

METHODS

Patient population: From February 1987 through April 1988, 50 patients were treated with reperfusion therapy (Table I) for acute myocardial infarction and were prospectively randomized to <24 hours (group 1) or ≥72 hours (group 2) infusion of intravenous heparin. To be eligible for randomization, the patients had to have a diagnosis of acute myocardial infarction with chest pain lasting >20 minutes, unrelieved with sublingual nitroglycerin and electrocardiographic evidence of injury with ≥1 mm of ST-segment elevation in ≥2 contiguous leads. All patients required emergency cardiac catheterization and underwent reperfusion therapy.

Patients were not eligible for randomization if they had an unsatisfactory angiographic result after reperfusion therapy, which included complex dissections,[9] residual filling defects, less than Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow pattern or >50% visual estimate of residual stenosis. All patients were clinically stable at the time of periaccess sheath removal, which was ≤24 hours after acute intervention. Randomization to either a brief (<24 hours) or prolonged (≥72 hours) infusion of heparin was performed at the time of sheath removal. During this same 14-month period a total of 164 patients underwent emergency cardiac catheterization for acute myocardial infarction. The majority (69%) were excluded from the current trial either because of failure to meet prespecified angiographic criteria or clinical instability in the first 24 hours.

Catheterization procedure: Patients underwent cardiac catheterization if they met the criteria already de-

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TABLE I Baseline and Treatment Characteristics

	Group 1 (n = 25)	Group 2 (n = 25)
No. male (%)	21 (84)	15 (60)
Age (yrs)	55 ± 9	54 ± 10
Infarct coronary artery		
LAD	10	10
LC	4	2
Right	11	13
Total occlusions	11	11
Thrombolytic alone	6	4
IV thrombolytics ± PTCA	14	15
Streptokinase	3	1
t-PA	6	7
t-PA and urokinase	5	7
Percent infarct vessel stenosis	30 ± 13	28 ± 12
Fibrinogen nadir (mg/dl)	170	142

There were no significant differences ($p < 0.05$) at baseline for the 2 groups.
IV = intravenous; LAD = left anterior descending; LC = left circumflex; PTCA = percutaneous transluminal coronary angioplasty; t-PA = tissue plasminogen activator.

scribed. If the patients were eligible for one of the Thrombolysis and Angioplasty in Acute Myocardial Infarction protocols, they received either tissue plasminogen activator (t-PA), urokinase or a combination of both, before emergency catheterization. Other patients received intravenous streptokinase or no thrombolytic therapy before this initial catheterization.

Using the percutaneous femoral technique, arterial and venous sheaths were inserted. At the time of obtaining vascular access, 5,000 U of intravenous heparin was administered. Initial injections of the coronary arteries were reviewed, and if an angioplasty was performed, an additional 5,000 U of heparin was administered. The patients received heparin boluses of 5,000 U hourly during the catheterization procedure.

At the conclusion of the procedure, the sheaths were secured with sutures to the access site and the patient received a heparin infusion to maintain the partial thromboplastin time at 2 times control (maximum up to 2.5 times control). The sheaths were withdrawn 24 hours after the acute catheterization. The heparin was discontinued for 2 to 4 hours before sheath removal. At this time, patients were eligible for randomization if they did not fulfill the angiographic exclusion criteria outlined previously. If the patient was randomized to a brief infusion (group 1) the heparin was not continued. Patients randomized to a prolonged infusion (group 2) were restarted receiving heparin therapy with an initial bolus of 3,000 to 5,000 U, followed by 800 to 1,200 U/hour, adjusted to maintain the partial thromboplastin time to 2 times control. Patients also received 325 mg of aspirin/day, diltiazem 30 to 60 mg 4 times/day and intravenous or oral nitrate therapy.

Patients had 12-lead electrocardiograms performed after reperfusion therapy and daily for 3 days. Creatinine kinase levels with MB isoenzyme analysis were performed every 8 hours for the first 24 hours and as clinically indicated during the hospitalization.

Endpoints evaluated during the study included chest pain felt to be ischemic in origin with documented electrocardiographic changes. Urgent recatheterization was then performed, documenting whether restenosis or reocclusion of the infarct-related artery had occurred. Reocclusion was defined as TIMI grade 0 or 1 on repeat cardiac catheterization and the percent residual stenosis was determined by caliper method. The amount and site of bleeding were also evaluated with serial hematocrits and the number of blood transfusions was recorded. A significant bleeding complication was defined as requiring ≥2 units of packed red blood cells. Patients were allowed to cross over to the other treatment group if recurrent ischemia or significant bleeding endpoints were reached.

RESULTS

Patient characteristics: The baseline clinical and angiographic characteristics of the randomized patients were similar for the 2 groups and are listed in Table I. The groups of patients randomized to a brief or prolonged infusion of heparin were comparable in age, male sex, infarct artery, type of intravenous thrombolytic agents used, number of total occlusions and percent visual estimate of residual stenosis after reperfusion therapy.

Acute reocclusions: Four patients had documented reocclusions on follow-up catheterization and were evenly divided between both groups. Three of the 4 patients had recurrent symptoms and electrocardiographic changes suggestive of ischemia before the follow-up heart catheterization, of which only 1 was successfully recanalized with angioplasty. Only 40 of the 50 patients consented to follow-up catheterization. Of the 10 patients in whom follow-up catheterization was not performed, exercise thallium scintigraphy or exercise radionuclide ventriculography was performed. There was no evidence of recurrent ischemia that would suggest restenosis in any patient.

Bleeding complications: There were no patients in group 1 who had significant bleeding (defined as the need for transfusion of ≥2 units of packed red blood cells). In group 2, 6 patients had significant bleeding, requiring discontinuation of heparin. A similar number of patients received thrombolytic agents in both groups. Of the 6 patients who had bleeding complications, 5 were women, and 5 had received thrombolytic agents before the initial catheterization. One patient received both intracoronary and intravenous streptokinase, and 1 patient received a combination of intravenous urokinase and t-PA. The other 3 had received intravenous t-PA. Sites of bleeding included the periaccess site, genitourinary (hematuria) and the gastrointestinal tract. No cases of intracerebral hemorrhages were noted.

DISCUSSION

The optimal prophylactic medical treatment after successful reperfusion therapy to maintain coronary artery patency is controversial, because in the previous trials that have used thrombolytic agents or angioplasty, or both, intravenous heparin has been continued for at least 72 hours after intervention, and usually until hospital discharge.[1-3] In the studies evaluating primary angioplasty for the treatment of acute myocardial infarc-

tion, the incidence of late reocclusion has ranged from 2 to 17%.[10-12] Treatment with intravenous thrombolysis has resulted in late reocclusions ranging from 5 to 45%.[1,13-15] Virtually all these patients have been treated aggressively with medical therapy including heparin and aspirin, and still a significant number of patients have documented reocclusion or recurrent ischemic events during the initial hospitalization.

Therefore, we have hypothesized that in those patients who have a minimal residual stenosis and who have no angiographic evidence of dissection or thrombus, there might not be additional benefit with a prolonged heparin infusion. In this group of patients, the use of heparin may be detrimental secondary to the risk of hemorrhage. We undertook this pilot trial to evaluate heparin's role in preventing reocclusion as well as the incidence of bleeding complications in patients undergoing successful reperfusion therapy.

In this randomized pilot study, the prolonged use of heparin did not appear to prevent reocclusion, as a similar proportion (8%) of patients in both groups had documented rethrombosis on follow-up catheterization. All patients had received heparin therapy for at least the initial 24 hours and the randomization was performed after this time. We attempted to eliminate patients who may have had subclinical thrombus formation at the time of the initial catheterization or who may have had recurrent ischemic events within the first 24 hours. It has been shown that with elective angioplasty and treatment with t-PA during acute myocardial infarction, recurrent ischemic events occur most frequently within the first 24 hours.[1,16] After elective angioplasty, full anticoagulation for 24 hours was found to be beneficial in patients both with and without angiographically visible thrombus present.[16] Although an angiogram may not demonstrate filling defects to be present, a residual thrombus was likely present. Therefore, in the control group, 24-hour heparin therapy was instituted. The results of our pilot study suggest that beyond this time interval, heparin does not appear to be of any added benefit in a group of patients who were at low risk of reocclusion by clinical and angiographic criteria.

A significant number of patients had bleeding complications in the group treated with prolonged heparin therapy. Greater than 20% of our patients who were treated with ≥72 hours of heparin required transfusion of ≥2 units of packed red blood cells and discontinuation of anticoagulation. Of the 6 patients with significant bleeding difficulties, 5 were women and 5 had received thrombolytic agents before the initial catheterization. All of the blood loss was confined to periaccess site bleeding or gastrointestinal or genitourinary sources. Similarly, the TIMI trial[13] reported a >15% incidence of bleeding events in both the patients treated with t-PA or streptokinase. All their patients had a pretreatment catheterization as well as subsequent prolonged intravenous heparin therapy. In the European Cooperative Study,[3] in which patients were treated with t-PA, heparin, aspirin and long-term coumadin therapy, there was a 23% incidence of significant bleeding complications in those treated without early cardiac catheterization, and a 41% incidence of bleeding in those undergoing invasive evaluation.

In our study, a similar number of patients in both groups received thrombolytic therapy. Therefore, it is of interest that only the group of patients treated with prolonged heparin therapy had significant blood loss recorded. Larger randomized studies are now being performed that will evaluate the use of prolonged heparin therapy in maintaining infarct artery patency in patients undergoing thrombolytic therapy alone. Both the Third International Study of Infarct Survival and Gruppo Italiano per lo Studio della Supravivenza Nell'Infarto Miocardioco trials are evaluating the use of high-dose subcutaneous heparin (12,500 U twice daily) in patients treated with intravenous streptokinase or t-PA and its effect on the in-hospital and long-term outcomes. If shown to be effective for reducing reinfarction, the use of subcutaneous heparin, as compared to the intravenous route, may reduce the risk of significant bleeding noted in the current and previous studies.[1,2] The recent Thrombolysis and Angioplasty in Acute Myocardial Infarction trial has demonstrated the lack of need for intravenous heparin bolus at the initiation of t-PA, and the avoidance of early heparin may also be effective in reducing hemorrhagic risk.[17]

A major limitation of our study is the number of patients. We did not attempt to detect a significant reduction in the rate of reocclusion with prolonged heparin therapy because the number of patients required to do this was beyond the scope of our study. To detect a 50% reduction in reocclusion with a 90% power, an α error of 0.05 and a β error of 0.10 would require 1,100 patients. Therefore, larger randomized control studies are needed to verify whether prolonged heparin therapy reduces the rate of reocclusion and would justify the significant bleeding risk determined in our study. The other limitations were that only 80% of our patients had a repeat coronary angiographic study at the time of hospital discharge, and we focused on a low-risk subgroup, as identified by clinical and angiographic criteria. Silent reocclusions may have occurred in the other 10 patients. Exercise tomographic thallium scintigraphy as well as exercise multigated blood pool images were performed in all these patients and no evidence of ischemia was demonstrated. This does not, however, rule out silent reocclusions with adequate collaterals. Two of these 10 patients developed recurrent symptoms of angina pectoris within 6 months, and had evidence of periinfarct ischemia on repeat thallium testing. Repeat cardiac catheterization demonstrated restenosis but not reocclusion in both these patients and repeat angioplasty was performed with resolution of the symptoms.

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