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High Dose Bolus Heparin as Initial Therapy Before Primary Angioplasty for Acute Myocardial Infarction: Results of the Heparin in Early Patency (HEAP) Pilot Study

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Objectives. **We sought to determine the effect of high dose intravenous bolus heparin on early coronary patency before primary angioplasty.**

Background. **Early coronary angiography after thrombolysis for acute myocardial infarction has shown better patency when intravenous heparin is used as an adjunct. The present study explores whether heparin alone can induce reperfusion.**

Methods. **In the Heparin in Early Patency (HEAP) pilot study, 108 patients with signs and symptoms of acute myocardial infarction <6 h eligible for primary angioplasty received a single intravenous bolus of 300 U/kg of heparin together with aspirin (160 mg chewed) in the emergency room. The median dose of bolus heparin given was 27,000 U. Patency of the infarct-related artery (IRA) was assessed by coronary angiography at a median of 85 min after the heparin bolus.**

Results. **In 55 patients (51%, 95% confidence interval 38% to 64%), Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 was observed at 90 min: TIMI flow grade 3 in 33 patients (31%); TIMI flow grade 2 in 22 (20%). Thirty-two (64%) of 50 patients with symptoms ≤2 h had TIMI flow grade 2 or 3 versus 23 (40%) of 58 patients with symptoms >2 h ($p = 0.02$). No significant bleeding was seen. Two patients (2%) died in the hospital. The patency results obtained in patients treated with the high dose bolus heparin were compared with those in 108 patients from a large primary angioplasty database, who were treated with standard therapy, including aspirin but not intravenous heparin, and were matched for clinical and angiographic characteristics with the HEAP pilot study patients. They showed an 18% patency rate ($p < 0.001$) of the IRA (TIMI flow grade 3 in 9%, TIMI flow grade 2 in 9%) before primary angioplasty.**

Conclusions. **Early therapy with high dose heparin is associated with full coronary reperfusion in a considerable number of patients with acute myocardial infarction, especially in those treated early (<2 h). This simple, inexpensive, probably safe and easily antagonizable treatment may be an attractive first treatment of acute myocardial infarction both before and during the hospital stay in conjunction with primary angioplasty.**

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Reperfusion therapy has become the cornerstone in the early treatment of acute myocardial infarction. Both pharmacologic therapy with thrombolysis (1,2) and primary angioplasty (3,4) can be used to achieve reperfusion of the infarct-related coronary artery. Thrombolysis has the disadvantages of bleeding complications, thrombin generation and partial efficacy, whereas primary angioplasty is successful in >90% of patients but has logistic limitations, including the inherent delay ("door to balloon time") during which no specific reperfusion therapy can be instituted. However, the introduction of primary angioplasty as an accepted therapy makes the testing of new reperfusion strategies or their adjuncts possible.

For >30 years, the role of heparin in the treatment of acute myocardial infarction has been controversial with regard to safety and efficacy. There is a large interindividual dose-response variability for heparin, making the efficacy of heparin unpredictable. Since the introduction of thrombolytic therapy for acute myocardial infarction, the heparin controversy has persisted until the publication of the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) trial results (1,2). Heparin, 5,000 U intravenously, followed by infusion at an activated partial thromboplastin time (APTT) between 60 and 85 s in conjunction with front-loaded tissue-type plasminogen activator (t-PA) resulted in the highest 90-min patency rate and subsequently the lowest mortality rate. Although the addition of intravenous heparin to streptokinase resulted in a trend toward improved patency, it did not lead to better survival than that with subcutaneous heparin (2).

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Abbreviations and Acronyms

APTT = activated partial thromboplastin time
ECG = electrocardiographic
HEAP = Heparin in Early Patency
IRA = infarct-related artery
ISIS = International Study on Infarct Survival
PTCA = percutaneous transluminal coronary angioplasty
TIMI = Thrombolysis in Myocardial Infarction
t-PA = tissue-type plasminogen activator

Compared with subcutaneous heparin, intravenous heparin did not prevent reocclusion in the GUSTO and other trials (5), suggesting that intravenous heparin facilitates early reperfusion rather than preventing reocclusion.

High dose heparin alone may induce lysis of experimental carotid artery thrombi, albeit in a lower percentage of patients than t-PA (6). Unfractionated heparin infusion can also enhance fibrinolysis in healthy volunteers (7).

In the present report we describe our initial experience with high dose bolus heparin as a first treatment in patients with an acute transmural myocardial infarction eligible for primary angioplasty treated with aspirin but not with thrombolysis. A heparin dose of 300 U/kg was chosen on the basis of the experience of cardiac surgeons. This high dose has been used for years before cardiopulmonary bypass. In the present study, the infarct-related artery patency before primary angioplasty was used to test the efficacy of high dose bolus heparin given at hospital admission together with aspirin. The results of this clinical trial were compared with those in a matched control group from a large primary angioplasty data base.

Methods

Patients. The Heparin in Early Patency (HEAP) protocol was approved by the ethical review committees of the four participating hospitals (North Colorado Medical Center, Greeley, Colorado; and Free University Hospital, Amsterdam; Weezenlanden Hospital, Zwolle; and University Hospital, Nijmegen, The Netherlands).

To study the objective, a pilot trial consisting of 100 patients was designed. Given the reported spontaneous reperfusion rate of 10% to 20%, a reliable patency rate with 100 patients treated with high dose bolus heparin could be expected in 100 patients.

Patients ≤75 years old with symptoms suggestive of an acute myocardial infarction ≤6 h in duration and electrocardiographic (ECG) abnormalities of ≥2-mm ST segment elevation in two or more contiguous leads were eligible for entry in the study. Patients with contraindications to thrombolysis, heparin or aspirin or those unable to undergo cardiac catheterization were excluded, as were those in cardiogenic shock.

After informed consent was obtained for the experimental therapy and the subsequent invasive procedure, 160 mg of aspirin was chewed. Immediately thereafter a single intravenous bolus of 300 U/kg body weight of heparin was administered. No thrombolytic agent was given. Intravenous beta-blockade or nitrates, or both, were used as clinically indicated.

Coronary angiography and rescue procedures. Coronary angiography was performed as soon as possible after bolus heparin therapy. Patency of the infarct-related artery (IRA) was scored according to Thrombolysis in Myocardial Infarction (TIMI) flow grade (8) by two independent experienced angiographers (G.V., F.Z.) in the angiographic core laboratory. In case of disagreement, the opinion of a third angiographer was decisive. Angiography was repeated at hospital discharge at two of the participating centers. During both procedures, left ventriculography was performed in the right anterior oblique view to calculate left ventricular ejection fraction.

If IRA patency at first angiography was TIMI flow grade 0 to 1 or less, primary angioplasty was performed. If angioplasty was not an option, emergent coronary artery bypass graft surgery was performed, or intracoronary streptokinase was delivered at a rate of 4,000 U/min for a maximum of 1 h. If infarct-related artery patency was TIMI flow grade 2 or 3, the decision to perform primary angioplasty was left to the discretion of the attending operator.

Follow-up treatment. Heparin therapy was started in all patients after the APTT had reached 2.0 to 2.5 times the control value. Aspirin, 80 mg daily, was given, as was heparin at an APTT of 2.0 to 2.5 times the control value for 48 h. Beta-blockade was continued unless contraindicated, and angiotensin-converting enzyme blockade was initiated when indicated. Revascularization was performed on clinical not angiographic grounds, except for left main coronary artery disease.

Control group. To compare the patency data obtained in the HEAP pilot study, angiograms of selected patients from the large Zwolle primary angioplasty data base, which contains the data of >800 patients, were studied. These patients had undergone primary angioplasty without pretreatment with intravenous heparin in the emergency room. Patients were matched for age, gender, IRA, time to admission and door to balloon time with the HEAP pilot study patients. Patency of the IRA before angioplasty was scored as previously described in the core laboratory by the same angiographers, who were unaware of the initial treatment.

Statistical analysis. The statistical methods used in this analysis are given where appropriate.

Results

Patients. Between November 1993 and June 1996, 108 patients were enrolled in the HEAP pilot study, not 100 patients as originally planned (see Methods). The baseline characteristics of the patients are shown in Table 1. Doses of bolus heparin given varied from 10,000 to 40,000 U (median 27,000). The bolus injection was completed in 106 (98%) of 108 patients. In one patient, heparin infusion was discontinued after 10,000 U, when hypotension occurred, which later proved to be cardiogenic shock. Another patient refused further therapy after 10,000 U of intravenous heparin had been given

Table 1. Baseline Characteristics of Heparin and Early Patency Pilot Study Patient and Control Groups

	HEAP Pilot Study Group (n = 108)	Control Group (n = 108)
Median age (yr)	59	59
Range	34–75	29–75
Men	84%	84%
Median time from 1st sx to tx (h)	2.2	2.2
Range	0.3–6.0	0.8–6.0
Anterior infarction (no. of pts)	64	64
Inferior infarction (no. of pts)	44	44

HEAP = Heparin in Early Patency; sx = symptoms; tx = treatment.

Table 2. Patency at 90 Minutes by Coronary Artery: Heparin in Early Patency Pilot Study

	TIMI Flow Grade		
IRA	0 or 1	2 or 3	Total
LMCA	1	0	1
LAD	29	34	63
LCx	5	6	11
RCA	18	15	33
Total	53	55	108

IRA = infarct-related artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction.

because of complete relief of pain. Both patients proved to have an open IRA.

Patency at 90 min. The median time interval between bolus heparin therapy and coronary angiography was 85 min (range 30 to 120 min). In 55 patients (51%, 95% confidence interval 38% to 64%), TIMI flow grade 2 or 3 was seen: TIMI flow grade 3 in 33 patients (31%); TIMI flow grade 2 in 22 (20%). Of 50 patients with symptoms ≤2 h in duration, 32 (64%) had TIMI flow grade 3 (n = 21) or 2 (n = 11) versus 23 (40%) of 58 patients (12 with TIMI flow grade 3, 11 with TIMI flow grade 2) with symptoms ≥2 h in duration (p = 0.02, chi-square test) (Fig. 1). There were no significant differences in age (59 ± 9 years [mean ± SD] for TIMI flow grade 0 or 1 vs. 60 ± 10 years for TIMI flow grade 2 or 3), gender or receipt of beta-adrenergic blocking agents (43% and 47%, respectively) and nitrates (94% and 100%, respectively). The 90-min patency rates are shown in Table 2.

Rescue procedures. The 53 patients with TIMI flow grade 0 or 1 were eligible for rescue procedures. In 47 patients primary angioplasty was performed and was successful in all but two. In two other patients, balloon angioplasty was not considered feasible: Intracoronary streptokinase was given successfully in one patient, and coronary atherectomy was performed in the other, resulting in full reperfusion. In one other patient, emergent coronary artery bypass graft surgery was carried out successfully. Finally, in three patients with failed reperfusion after high dose bolus heparin, the attending physician decided that a rescue procedure was not indicated. These patients had distal coronary occlusion. Thus, the overall reperfusion success rate was 95% (103 of 108).

In 15 of 20 patients with TIMI flow grade 2, the operator decided to perform primary angioplasty, which was successful in 13. In one patient, nonocclusive coronary dissection occurred, followed by elective coronary surgery, and one patient with failed angioplasty underwent rescue coronary atherectomy.

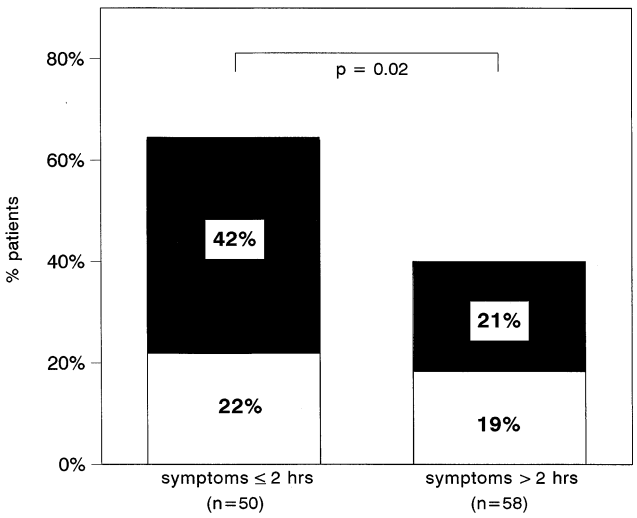
In 22 of 35 patients with TIMI flow grade 3, the operator decided to perform primary angioplasty, which was successful in all. Of 13 remaining patients with TIMI flow grade 3, 3 underwent emergent coronary surgery immediately after first angiography. In the 10 remaining patients, the operator decided not to perform primary angioplasty on angiographic grounds.

Thus, primary angioplasty was performed in 84 (78%) of 108 patients and not in 34 (22%).

Clinical follow-up. At 90 min after high dose bolus heparin, the APTT exceeded 120 s in all 106 patients who received the full dose of heparin. Mean peak creatine kinase was 881 U/liter (range 28 to 5,400). Eight patients (7%) did not have an infarction by elevated enzyme levels (less than twice the upper limit of creatine kinase). No cerebral bleeding was seen nor was any bleeding leading to blood transfusion observed during the entire hospital phase. Two patients (2%) died: one after elective coronary surgery 9 days after hospital admission; one after recurrent myocardial infarction 3 days after admission. Repeat angioplasty was necessary in seven patients (7%) and elective coronary surgery in seven (7%) during the hospital stay.

Of 29 patients undergoing predischarge coronary angiography, 25 patients (86%) had TIMI flow grade 3, and 3 (10%)

Figure 1. Patency of the IRA (TIMI flow grade 2 **[open areas]** or 3 **[solid areas]**) 90 min after high dose bolus heparin in the HEAP pilot study in patients with symptoms ≤2 h versus those with symptoms >2 h.



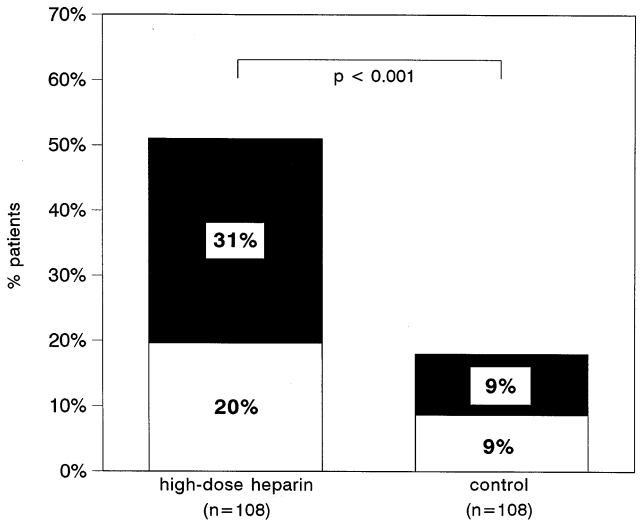


Figure 2. Patency of the IRA (TIMI flow grade 2 **[open areas]** or 3 **[solid areas]**) 90 min after high dose bolus heparin in the HEAP pilot study compared with the patency rate before primary angioplasty in the age- and gender-matched control group not receiving high dose bolus heparin.

had TIMI flow grade 2. All but three of these patients had undergone percutaneous transluminal coronary angioplasty (PTCA) in the acute phase. Reocclusion of initially open vessels was observed in 1 (4%) of 29 vessels. In 21 patients with two analyzable left ventricular angiograms and with a persistently open IRA, the left ventricular ejection fraction increased from 56 ± 9% to 59 ± 9% ($p = 0.07$, Student t test).

Comparison with control patients. The 108 patients from the Zwolle angioplasty data base were matched for clinical and angiographic characteristics as described previously, and their baseline characteristics are shown in Table 1. The control patients had been treated from February 1993 to April 1996. As shown in Figure 2, the control patients showed an 18% patency rate ($p < 0.001$ vs. HEAP pilot study patients, chi-square test) of the IRA (TIMI flow grade 3 in 10 patients [9%], TIMI flow grade 2 in 9 [9%]). Of 42 patients with ≤2-h symptom duration, 9 (21%) had TIMI flow grade 3 (n = 5) or 2 (n = 4) versus 10 of 66 patients (15%) (5 with TIMI flow grade 3, 5 with grade 2) with symptoms >2 h ($p = 0.56$, chi-square test).

Discussion

In the HEAP pilot study, a positive influence of high dose bolus heparin therapy on early IRA patency became apparent. It is unknown whether this effect approximates the results of well established intravenous reperfusion strategies such as streptokinase or t-PA (TIMI flow grade 2 or 3 at 90 min in 57% and 81% respectively [2]). However, compared with a well matched primary angioplasty control group not receiving high dose bolus heparin, the high dose bolus heparin appears to be superior (51% vs. 18% before angioplasty).

Mode of action of high dose bolus heparin. The exact mechanism of early patency using high dose bolus heparin is unknown. High dose heparin achieves lysis of experimental carotid artery thrombi (6), and a bolus of 5,000 U unfractionated heparin enhances fibrinolysis in healthy individuals (7). Intravenous heparin together with aspirin may induce coronary reperfusion by blocking ongoing thrombus formation. In the Late Assessment of Thrombolytic Efficacy (LATE) trial, intravenous heparin, although not randomized, together with aspirin was associated with an 8.7% mortality rate compared with 12.9% for aspirin alone (9). This finding was independent of the use of thrombolytic therapy. However, in the International Study on Infarct Survival (ISIS)-2 trial (10), patients randomized to aspirin, but not to thrombolysis, additional intravenous heparin, also not randomized, did not demonstrate improved survival compared with those without heparin (10.9% and 10.1%, respectively). It should be emphasized that the initial heparin dose was much lower than that in the present study.

Early treatment with heparin in the HEAP pilot trial resulted in better reperfusion than later treatment. Apparently, the nature of very fresh clots makes them accessible for heparin. In general, heparin is ineffective in clot-bound thrombin, but this finding may not be true for thrombin in very fresh arterial thrombi. Recently, preliminary data from a small randomized trial showed a 50% preangioplasty patency rate in 22 patients with an acute myocardial infarction given high dose bolus heparin (300 U/kg) at admission versus only 13% in 23 patients given placebo (11). Significant bleeding was not observed in that trial. Also, other nonthrombolytic strategies may induce coronary recanalization before primary angioplasty for acute myocardial infarction. Abciximab, a monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor, given to patients in the catheterization laboratory just before primary angioplasty, proved to induce the process of recanalization within 10 min from the start of therapy (12).

The outcome of the HEAP pilot study may reflect spontaneous reperfusion in selected patients, although in the control group this was limited to ~20%. In the early trials with intracoronary streptokinase, the administration of heparin and aspirin before angiography was uncommon, and the rate of spontaneous coronary reperfusion was found to be 15% to 20% (8,13). This rate is much lower than the early patency rate observed in the HEAP pilot trial. After publication of the ISIS-2 trial (10), early administration of aspirin became standard therapy. Heparin treatment in conjunction with thrombolysis has become popular since the introduction of t-PA as a thrombolytic strategy (2,14–16). Given these established treatment regimens as standard adjuncts to reperfusion therapy, the true early spontaneous reperfusion rate in modern cardiology will be difficult to determine and possibly not attainable secondary to ethical considerations. Finally, it is possible that the remarkable findings of the HEAP pilot study are attributable to the use of aspirin, but early angiographic patency studies with aspirin alone do not exist.

Bleeding risk of high dose bolus heparin. The HEAP pilot study is too small to be conclusive about the safety of a single

high dose bolus of heparin in acute myocardial infarction. In cardiac surgery, from which the heparin dosing in this study was adopted, cerebral bleeding is very rare. Most strokes after heart surgery are probably embolic. The incidence of fatal and major bleeding due to heparin in the absence of thrombolytic therapy is 0.05% and 0.8%/day of treatment (17). Fatal bleeding with 2 days of heparin therapy can be expected in 0.1% of patients and major bleeding in 1.6% and is probably less than that with thrombolysis, where fatal hemorrhagic stroke occurs in 0.5% of patients (1).

Possible advantages of high dose bolus heparin in acute myocardial infarction. The advantages of high dose bolus heparin in the early treatment of acute myocardial infarction are numerous: 1) The need for primary angioplasty may be reduced. Only 78% of patients in the HEAP pilot trial had the procedure compared with >90% for the usual primary PTCA (3,4). This reduced need may also reduce the cost of primary angioplasty for acute myocardial infarction, which is currently similar to (18) or even lower than that for thrombolytic therapy (19). Furthermore, heparin bolus administration is easy, can be given before hospital admission and does not necessarily need ECG guidance. It is inexpensive, and a single dose is probably safe. In case of bleeding, heparin therapy is easily and definitely antagonizable. The apparent ability of heparin to induce reperfusion in some patients raises the possibility that heparin may significantly augment the efficacy of thrombolytic agents when it is given in higher doses than have been used previously. It is intriguing to speculate as to the efficacy of a large dose of heparin combined with a small dose of a thrombolytic drug. Finally, in patients ineligible for thrombolysis, high dose bolus heparin may be an attractive alternative.

Conclusions. In patients with acute transmural myocardial infarction, early high dose bolus heparin together with aspirin is associated with a favorable coronary patency rate 90 min after initiation of therapy. This finding may be of interest for early prehospital treatment of infarction for patients ineligible for thrombolytic therapy and for patients awaiting primary angioplasty of the IRA. The efficacy of this early, single high dose bolus heparin will be compared with a low dose bolus in patients with an acute myocardial infarction awaiting primary angioplasty in a large randomized angiographic trial that has recently been initiated in The Netherlands.

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