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COOPERATIVE STUDIES

Correlation Between Level of Heparinization and Patency of the Infarct-Related Coronary Artery After Treatment of Acute Myocardial Infarction With Alteplase (rt-PA)

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Background and Objectives. The conjunctive use of intravenous heparin may influence the efficacy of alteplase for coronary thrombolysis in patients with acute myocardial infarction. In this study we examined the relation between the level of intravenous anticoagulation with heparin and sustained coronary artery patency in a subgroup of patients of the European Cooperative Study Group (ECSG) trial.

Methods. In the ECSG trial, patients treated with alteplase and aspirin were randomized to concomitant fixed doses of intravenous heparin (a bolus dose of 5,000 U followed by a continuous infusion of 1,000 U/h or placebo). The current study group comprised 149 of 324 ECSG patients allocated to heparin therapy and 132 of 320 ECSG patients allocated to placebo administration who had both an interpretable coronary angiogram obtained within 6 days of treatment and sufficient plasma samples to assess the level of anticoagulation. Activated partial thromboplastin times, fibrinogen and D-dimer levels were determined on plasma samples at baseline and at 45 min and 3, 12, 24 and 36 h after the start of alteplase administration.

Results. The coronary artery patency rate was higher in patients allocated to heparin therapy than in those allocated to placebo (80% and 71%, respectively, p = 0.05). Patients allocated to heparin were classified into three subgroups: 48 patients (32%) with all activated partial thromboplastin times at least twice their own baseline value (optimal anticoagulation), 40 patients (27%) with the lowest activated partial thromboplastin time at 3, 12, 24 or 36 h between 130% and 200% of the baseline value (suboptimal anticoagulation) and 61 patients with at least one activated partial thromboplastin time <130% of baseline (inadequate anticoagulation). In the heparin group, coronary artery patency correlated with the level of anticoagulation: 90%, 80% and 72%, respectively, in patients with optimal, suboptimal and inadequate anticoagulation (p = 0.02, optimal vs. inadequate anticoagulation). Heparin administration was associated with a smaller reduction in fibrinogen and a smaller increase in D-dimer level during and after alteplase administration. No correlation was found between fibrinogen or D-dimer levels and coronary artery patency. No intracerebral hemorrhage occurred in these patients; however, bleeding was more frequent in the subgroup with optimal anticoagulation (p = 0.05).

Conclusions. Intense anticoagulation with intravenous heparin enhances coronary artery patency after alteplase treatment of acute myocardial infarction.

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Intravenous thrombolytic therapy with streptokinase, alteplase or anistreplase reduces mortality in patients with evolving acute myocardial infarction (1–4). However, the optimal regimen for thrombolytic therapy has yet to be defined. In particular, the need for continued anticoagulation after thrombolytic therapy remains uncertain. Administration of heparin to patients treated with alteplase does not further improve coronary artery patency as determined by coronary angiography at 90 min (5). However, among patients given alteplase, the patency rate after 18 h (6), 57 h (7) or 2 to 5 days (8) was higher in those with than in those without additional concomitant treatment with intravenous heparin. Although different doses of aspirin were given in these three studies (80 mg, none and 325 mg/day, respectively), the results support the hypothesis that intravenous heparin improves sustained coronary artery patency induced with alteplase. In the European Cooperative Study Group (ECSG) trial (8), fixed doses of heparin were used to maintain double blinding in comparison with placebo. Because the amount of heparin needed to achieve adequate anticoagulation varies among subjects, it is likely that fixed heparin doses will result in optimal anticoagulation in some patients and in inadequate anticoagulation in others. Therefore, in the present study, the relation between the level of intravenous anticoagulation, as monitored by activated partial thromboplastin time assays, and subsequent coronary artery patency was analyzed in a representative subset of

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Table 1. Patient Entry

Patients (no.)	Treatment Group	
	Heparin	Placebo
Total in the ECSG trial (8)*	324	320
With no blood samples drawn for central hemostasis analysis†	168	168
With not enough activated partial thromboplastin times times to assess intensity of anticoagulation	3	12
With no angiography performed within 6 days	4	8
Total entered in present study‡	149	132

*After exclusion from analysis of eight patients for technical or administrative reasons. †Only the first 400 patients included in the European Cooperative Study Group (ECSG-6) trial were scheduled for serial blood sampling. ‡In 5 of the 149 patients allocated to heparin and 8 of the 132 patients given placebo, a second dose of alteplase was given before angiography. These patients were included in the analysis; it was assumed that the infarct-related vessel was occluded (Thrombolysis in Myocardial Infarction [TIMI] grade 0).

patients in the ECSG trial treated with alteplase and aspirin and concomitant fixed dose intravenous heparin or placebo (8).

Methods

Patient selection and treatment. Coagulation measurements were performed in a subset of patients in the heparin trial of the European Cooperative Study Group (ECSG-6) (Table 1). Patients aged 21 to 70 years were recruited according to well defined selection criteria similar to those in other European Cooperative Study Group trials (9–11). All patients were treated with alteplase, 100 mg (Actilyse, Boehringer Ingelheim, Ingelheim, Germany) administered intravenously as a 10-mg bolus dose followed by 50 mg over the 1st h and 40 mg over the next 2 h, and with aspirin, either as a 250-mg intravenous bolus dose (continental centers) or 300 mg orally (United Kingdom center) followed by 75 to 125 mg on alternate days in all centers. Patients randomized to heparin therapy were given an intravenous bolus dose of 5,000 U immediately after randomization followed by an infusion of 1,000 U/h. This dose remained unchanged and adjustment of the heparin dose according to hemostasis measurements was not allowed until coronary angiography. After angiography, investigators were free to continue or discontinue heparin administration. Heparin placebo (dilute albumin solution) was prepared in identical vials and given in the same way to patients randomized to placebo. All subjects entered into this study gave informed consent, and the study protocol has been approved by the institutional committees on medical research.

Study end points. The primary end point of the heparin trial of the European Cooperative Study Group was coronary artery patency as documented by angiography performed between 48 and 120 h after the onset of thrombolytic treatment. Secondary end points included recurrent ischemia and reinfarction (see later) and bleeding complications. The present analysis focuses on the contribution of the level of anticoagulation, as assessed by serial activated partial thromboplastin measurements, to primary and secondary end points.

Blood sampling and handling. The first 400 patients of a total of 652 patients from 19 centers in six European countries were scheduled for serial blood sampling. Blood samples were drawn before treatment allocation (baseline) and at 45 min, 3 h (end of alteplase infusion), 12 h, 24 h and 36 h after initiation of thrombolytic therapy. Tubes for blood collection contained 0.5 ml of sodium citrate (final concentration 0.011 mol/liter), and either aprotinin (final concentration 150 kIU/ml) or D-phenylalanyl-prolyl-arginine-chloromethylketone (PPACK, final concentration 0.002 mmol/liter) as, respectively, thrombin (12) and alteplase (13) inhibitor. Venous blood was collected from a free-flowing needle and without tourniquet, if possible. Sampling from indwelling catheters was allowed after the first 10 ml of blood was discarded. Within 20 min of blood collection the tubes were centrifuged at 2,000 *g* for 10 to 20 min and the platelet-poor plasma was stored below −20°C. For assessment of the level of anticoagulation, the baseline plasma sample and at least two of the four samples scheduled at 3, 12, 24 and 36 h after the onset of alteplase administration were required.

Hemostasis analyses. All laboratory analyses were performed centrally at the Center for Thrombosis and Vascular Research, Leuven, Belgium without knowledge of clinical or angiographic data. Activated partial thromboplastin times were determined in plasma samples collected on citrate and aprotinin, on an automated coagulation analyzer (ACL 810, Instrumentation Laboratory, Milan, Italy) with use of a micronized silica activated partial thromboplastin time reagent (Instrumentation Laboratory). The level of anticoagulation was assessed on the basis of the activated partial thromboplastin times of the samples collected 3, 12, 24 and 36 h after initiation of therapy. *Optimal anticoagulation* was defined as no activated partial thromboplastin time <200% of the patient's own baseline value in any sample collected at 3, 12, 24 or 36 h after initiation of therapy. Patients were considered to have *suboptimal anticoagulation* when the lowest activated partial thromboplastin time at 3, 12, 24 or 36 h was 130% to 200% of the baseline value. Patients were defined to have *inadequate anticoagulation* when the shortest activated partial thromboplastin time was <130% of the baseline value. It should be noted that the activated partial thromboplastin time, although generally used to assess the intensity of heparin therapy during therapeutic thrombolysis, can also be prolonged by fibrinogen degradation products or by inactivation of coagulation Factors V and VIII resulting from systemic plasmin generation and alpha$_2$-antiplasmin depletion.

Fibrinogen was determined on plasma collected on citrate and aprotinin by a fibrin polymerization time method (14)

Table 2. Demographic and Clinical Baseline Characteristics of Patients Entered Into the Present Study

	Treatment Group		Level of Anticoagulation in Heparin Group		
	Placebo (n = 132)	Heparin (n = 149)	Optimal (n = 48)	Suboptimal (n = 40)	Nonoptimal (n = 61)
Age (yr) (mean; range)	56; 26–70	56; 27–70	59; 25–70	54; 27–68	55; 33–69
Male	121 (92)	128 (86)	39 (81)	34 (85)	55 (90)
Anterior infarct	59 (45)	58 (39)	16 (33)	17 (43)	25 (41)
Previous infarct	3 (2)	10 (6)	3 (6)	3 (8)	4 (6)
History of angina	70 (54)	79 (80)	25 (52)	21 (53)	34 (56)
Right heart failure	2	2	1	0	1
Mild left heart failure	13	19	4	5	10
Overt left heart failure	0	1	1	0	0
Shock	1	5	2	1	2
Time from onset of symptoms to start of infusion (min) (median; range)	168; 45–392	168; 60–350	172; 75–345	159; 60–300	170; 60–350
Time from randomization to coronary angiography (h) (median; range)	77; 4–130*	82; 46–131	83; 46–125	80; 49–131	82; 48–119

*Three patients in the placebo group underwent early angiography at 4, 11 and 13 h, respectively, after the onset of thrombolytic treatment; without these patients the range would have been 45 to 130 h. Unless otherwise indicated, values are number of patients with percent of each group in parentheses.

with use of a semiautomated coagulation instrument (KC10, Amelung, Germany). D-dimer levels were determined in plasma samples collected on citrate and D-phenylalanyl-prolyl-arginine-chloromethylketone with use of a sandwich enzyme-linked immunosorbent assay (ELISA) based on a fibrin fragment D-dimer–specific capture monoclonal antibody and a fibrin fragment D-specific tag antibody (15).

Coronary angiography. Coronary angiography was scheduled between 2 and 5 days after the start of thrombolytic treatment. In the present ancillary study all patients were included who had angiography within 6 days after allocation.

The patency of the infarct-related vessel was assessed by a panel of five observers who had no knowledge of treatment allocation. Results are reported as Thrombolysis in Myocardial Infarction (TIMI) flow grades (16). Patients who were given a second dose of alteplase for clinical signs of reocclusion before the scheduled coronary angiography were considered to have TIMI grade 0 flow for the present analysis, irrespective of the result of angiography. If angioplasty had been performed, only the angiographic results obtained before this intervention were used in this study.

Recurrent ischemia and reinfarction. Clinical, electrocardiographic and serum enzyme evidence of recurrent ischemia and reinfarction were reviewed by an independent clinical event committee. Recurrent ischemic events were classified as reinfarction (characterized by recurrent increase in cardiac enzyme levels), unstable angina (angina with dynamic ST segment changes without enzyme increase) or other chest pain. Repeated administration of alteplase for clinical signs of reocclusion was allowed by the protocol.

Bleeding complications. Hemorrhagic complications were recorded in detail on case report forms according to preset criteria. Major hemorrhagic complications (need for transfusion, intracranial hemorrhage, retroperitoneal bleeding) were reviewed and further investigated by a central clinical events committee.

Statistical analysis. Analysis was performed with the Statistical Analysis System (SAS), version 6.09 on an IBM computer. The Fisher exact test was applied to categoric variables and the Wilcoxon rank sum test (Mann-Whitney) was used to compare numeric data between patient groups.

Results

A total of 652 patients were included in the heparin trial, of whom 8 were excluded from analysis because of technical or administrative reasons (8). Of the first 400 patients scheduled to enter the present substudy, 281 patients had adequate angiograms and a sufficient number of activated partial thromboplastin times available for the analysis. A complete set of activated partial thromboplastin times was available in 81% of the selected patients; 15% of the patients had only one activated partial thromboplastin time lacking. Of the 281 patients included in this study, 13 received a second dose of alteplase before angiography because of clinical signs of reocclusion (pain with ST segment elevation). There were 149 patients allocated to concomitant heparin therapy and 132 patients assigned to placebo (Table 1). Baseline characteristics in these two groups were well balanced (Table 2) and indistinguishable from those of the total population of the European Cooperative Study Group heparin trial described elsewhere (8). Although all patients allocated to heparin therapy received a 5,000-U heparin bolus and a continuous infusion of 1,000 U/h, an optimal level of anticoagulation, as specified in the Methods section, was achieved in only 48 (32%) of the 149 patients; 40 (27%) had a suboptimal level of anticoagulation and 61 (41%) had inadequate anticoagulation. Baseline characteristics were similar in these three subgroups (Table 2).

Hemostatic variables. Baseline (time 0) activated partial thromboplastin times, fibrinogen and D-dimer levels did not differ between patients allocated to placebo or heparin.

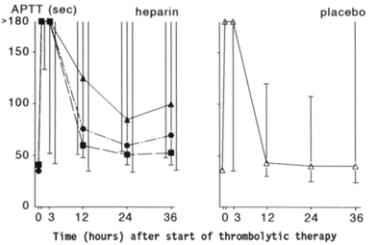

Figure 1. Activated partial thromboplastin times (APTT) in seconds (median ± 5 to 95 percentiles) at 0, 0.75, 3, 12, 24 and 36 h, in both treatment groups. The heparin group is subdivided on the basis of the activated partial thromboplastin times: (▲) optimal anticoagulation (n = 48, percentiles shown at **left**); (●) suboptimal anticoagulation (n = 40, percentiles shown in the **middle**) and (■) inadequate anticoagulation (n = 61, percentiles shown at **right**).

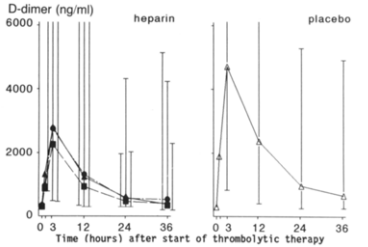

Figure 3. D-dimer levels (ng/ml; median ± 5 to 95 percentiles) at 0, 0.75, 3, 12, 24 and 36 h, in both treatment groups. The heparin group is subdivided on the basis of the activated partial thromboplastin times (see Fig. 1 for numbers and position of percentiles in different groups).

Toward the end of the infusion of alteplase (time = 3 h), activated partial thromboplastin times were prolonged in both the heparin and placebo groups (Fig. 1). By definition, after 12 h, the activated partial thromboplastin time remained prolonged in the subgroup of patients with optimal anticoagulation, whereas the value returned to near baseline levels in patients with inadequate anticoagulation.

During alteplase infusion, fibrinogen levels were reduced in both groups, to 65% and 60% at 3 h in the heparin and placebo groups, respectively (Fig. 2); thereafter, a gradual recovery of fibrinogen levels was observed. Fibrinogen levels did not correlate either with the level of anticoagulation or with coronary artery patency.

Most of the study patients (75%) had normal D-dimer levels (<500 ng/ml) at baseline. D-dimer levels significantly increased during and after thrombolysis in both the placebo and the heparin group, although the observed changes were less pronounced in the heparin group ($p = 0.0001$ at 3 h) (Fig. 3). In heparin-treated patients, D-dimer levels did not correlate with the level of anticoagulation or with patency.

Correlation between the level of anticoagulation and subsequent coronary artery patency. Concomitant intravenous administration of heparin with alteplase and aspirin was associated with a higher patency rate (TIMI grade 2 or 3) of the infarct-related artery than was administration of placebo (80% vs. 71%, respectively, $p = 0.05$, Fig. 4). Among the

Figure 2. Fibrinogen levels (median ± 5 to 95 percentiles) at 0, 0.75, 3, 12, 24 and 36 h in both treatment groups. The heparin group is subdivided on the basis of the activated partial thromboplastin times (see Fig. 1 for numbers and position of percentiles in different groups).

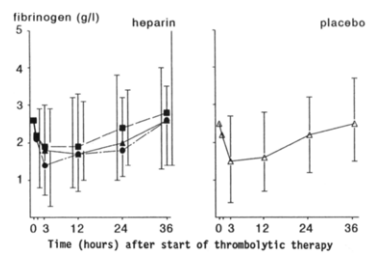

Figure 4. Coronary perfusion status (Thrombolysis in Myocardial Infarction [TIMI] grades 0 to 3) at angiography within 144 h in both treatment groups (heparin [n = 149], placebo [n = 132]) and in the heparin subgroups classified on the basis of activated partial thromboplastin times into those with optimal (n = 48), suboptimal (n = 40) and inadequate (n = 61) anticoagulation. The figures next to the bars present the percent of occluded vessels (TIMI grade 0 and 1). p values are for differences in TIMI grades 0 and 1 versus TIMI grades 2 and 3.

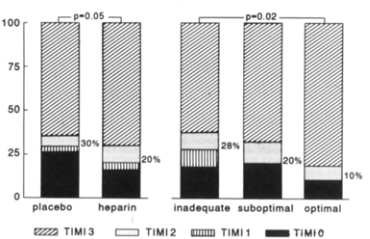

Table 3. Frequency of Recurrent Ischemic Events in Subgroups Classified by Level of Anticoagulation

	Placebo Group (n = 132)	Heparin Group*		
		Optimal (n = 48)	Suboptimal (n = 40)	Inadequate (n = 61)
Before angiography				
Reinfarction	0	0	0	1
Unstable angina	15	4	3	6
Other chest pain	5	1	1	1
After angiography				
Reinfarction	1	1	1	1
Unstable angina	12	6	4	3
Other chest pain	1	1	0	0

*See text for definitions of optimal, suboptimal and inadequate anticoagulation.

heparin-treated patients, coronary artery patency (TIMI grade 2 or 3) was 90% (43 of 48) in the subgroup with optimal anticoagulation compared with 80% (32 of 40) in those with suboptimal anticoagulation and 72% (44 of 61) in the subgroup with inadequate anticoagulation ($p = 0.02$, optimal vs. inadequate anticoagulation). A complete set (five blood samples) of activated partial thromboplastin times was available in 85%, 73% and 80%, respectively, of patients with optimal, suboptimal and inadequate anticoagulation.

In the placebo group, 22 patients had prolonged activated partial thromboplastin times; 8 were classified as having optimal and 14 as suboptimal anticoagulation by the definition used for patients allocated to heparin therapy. The patency rates in these patients were 50% (4 of 8) and 64% (9 of 14), respectively, compared with 73% (80 of 110) in placebo-treated patients without prolonged activated partial thromboplastin times. Eight patients in the placebo group were classified as having an occluded coronary artery (TIMI grade 0) because of symptoms that led to a second administration of alteplase.

Recurrent ischemia. Recurrent ischemia between the onset of thrombolytic treatment and angiography tended to be more frequent in the patients treated with placebo (17%) than in those given heparin (11%) (Table 3). However, no difference was apparent between the incidence of recurrent ischemia in the different subgroups.

Bleeding complications. Although no difference was apparent in bleeding complications between the heparin and placebo groups in this substudy, bleeding complications tended to be more frequent in the heparin group in the total patient population of the European Cooperative Study Group study (8). Within the heparin group of the present substudy bleeding complications were more frequent in patients with optimal than in those with inadequate anticoagulation (Table 4). The majority of complications were hematomas or prolonged bleeding at puncture sites. Intracerebral bleeding was not observed in the patients of this substudy.

Discussion

The need for early intravenous anticoagulation to maintain coronary artery patency after treatment with alteplase has been documented in three recent studies (6–8). The current substudy of the heparin trial of the European Cooperative Study Group shows that patency up to 6 days after initial therapy with alteplase is dependent on the actual level of anticoagulation. A 90% patency rate after alteplase therapy can be achieved by optimal anticoagulation with intravenous heparin, defined as activated partial thromboplastin times consistently above twice baseline values.

In patients with evolving myocardial infarction after thrombolytic therapy, the disrupted endothelium, the atherosclerotic surface and residual thrombi at the site of initial coronary occlusion represent potent thrombogenic stimuli that continue to activate the coagulation system. Furthermore, thrombolytic therapy appears to be associated with in vivo activation of the coagulation system (17–21). This may result in reocclusion of the diseased artery, and may explain the somewhat higher reocclusion rates after thrombolytic therapy with more fibrin-selective drugs such as alteplase, compared with agents that result in extensive fibrinogen depletion such as streptokinase or anistreplase. Heparin suppresses the enhanced fibrin generation during and after

Table 4. Bleeding Complications Between Allocation and Discharge in Subgroups Classified by Treatment Arm and Level of Anticoagulation

	Placebo Group (n = 132)	Heparin Group*		
		Optimal (n = 48)	Suboptimal (n = 40)	Inadequate (n = 61)
Patients with one or more bleeding complications	26	14	7	8
Major hematoma at puncture site	18	13	4	4
Major hematoma at other site	3	2	0	1
Prolonged bleeding at puncture site	3	2	0	0
Intracranial bleeding	0	0	0	0
Other	6	2	3	6

*See text for definitions of optimal, suboptimal and inadequate anticoagulation.

thrombolytic therapy with alteplase (22). In experimental animal models of thrombosis, thrombolysis with alteplase is enhanced by concomitant infusion of heparin (23,24). In the present study, heparin administration limited the increase in D-dimer during and after thrombolytic therapy, which supports the hypothesis that heparin reduces the extent of activation of the coagulation system in patients receiving thrombolytic therapy.

Level of anticoagulation and arterial patency. The present data from a representative subgroup of 281 patients participating in the double-blind heparin versus placebo trial by the European Cooperative Study Group (8) indicate that a fixed dose of 1,000 U of heparin/h provides adequate anticoagulation in only 32% of patients. A very high coronary patency rate (90%; 95% confidence interval 77% to 97%) was observed in patients with optimal anticoagulation, defined as an activated partial thromboplastin time >200% of baseline value at all measurements between 3 and 36 h, whereas patency in patients with inadequate anticoagulation was similar to that found in patients given placebo. Similarly, in the Heparin-Aspirin Reperfusion Trial (HART) (6) the activated partial thromboplastin time after 18 h was more prolonged in patients with a patent coronary artery than in those with an occluded artery (25). Thus, to maintain coronary patency up to 144 h, alteplase requires intense anticoagulation with intravenous heparin for at least 36 h.

Eight patients who received placebo were classified as having "optimal anticoagulation." It is likely that the activated partial thromboplastin times in these patients represent a prolonged effect of thrombolysis. It is noteworthy that in this subgroup fibrinogen levels were the lowest and D-dimer levels the highest in the placebo group (Fig. 3).

Recurrent ischemia. Surprisingly, no correlation was found between the level of anticoagulation and the incidence of recurrent ischemia. This finding can at least in part be explained by the relatively small number of patients but may support the hypothesis that, in addition to adequate anticoagulation, potent antiplatelet agents other than aspirin may be needed to prevent recurrent ischemia.

Bleeding complications. Conjunctive heparin and thrombolytic treatment slightly increased the risk for bleeding complications when the total group of heparin-treated patients in the European Cooperative Study Group trial is compared with the placebo group (8). In the present study, the frequency of bleeding complications, mainly hematomas at puncture sites, was higher in the subgroup with adequate anticoagulation than in patients with inadequate anticoagulation or in those receiving placebo.

Conclusions. The present study shows that, to sustain coronary patency, patients treated with alteplase require concomitant adequate anticoagulation with heparin. Whether this early and sustained patency will translate to a reduced mortality remains to be confirmed by large prospective studies using alteplase and controlled anticoagulation with heparin. The Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) trial (26) may help to clarify this issue.

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