Effect of heparin, aspirin or alteplase in reduction of myocardial ischemia in refractory unstable angina

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Effect of heparin, aspirin, or alteplase in reduction of myocardial ischaemia in refractory unstable angina

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399 out of 474 inpatients with unstable angina were monitored for 48 h and 97 of these were found to be refractory to conventional antianginal treatments and entered a randomised double-blind study. With the initial protocol heparin infusion or bolus were compared with aspirin; with a modified protocol, heparin infusion, the best of these three treatments, was compared with alteplase. Patients were monitored for 3 days after starting treatment and then observed clinically for 4 more days. On the first days of treatment heparin infusion significantly decreased the frequency of angina (by 84–94%), episodes of silent ischaemia (by 71–77%), and the overall duration of ischaemia (by 81–86%). Heparin bolus and aspirin were not effective. Alteplase caused small (non-significant) reductions on the first day only. Only minor bleeding complications occurred.

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Introduction

Can antithrombotic therapy control myocardial ischaemia? Heparin infusion but not aspirin alleviated refractory unstable angina,[1] but intracoronary or intravenous thrombolytic therapy has produced equivocal results in unstable angina.[2-7] In these studies the effectiveness of antithrombotic therapy was evaluated by considering anginal attacks only and not silent ischaemic episodes, which occur at high frequency (50–90%) in such patients.[8,9] Silent ischaemia is associated with a poor prognosis[8,9] and with increased risk of sudden death.[10] Since most episodes of ischaemia are asymptomatic, the frequency of angina may not reflect the severity of ischaemia.[11] We have investigated the effectiveness of heparin, aspirin, and thrombolytic therapy on anginal attacks and on silent ischaemia in patients with angina refractory to conventional treatments.

Patients and methods

Patients

474 patients admitted with unstable angina (defined as typical chest pain occurring at rest or on minimum effort associated with reversible ST segment elevation or depression of at least 0·1 mV 80 ms after J point, or a single episode of chest pain lasting 20 min or longer with serum concentrations of creatine kinase less than twice the upper limit of normal value) were eligible. The last painful episode could have occurred less than 24 h before admission. All eligible patients were treated orally with isosorbide dinitrate

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TABLE III—RESPONSE TO HEPARIN INFUSION OR BOLUS OR ASPIRIN

	Run-in days		Treatment days			Mean (SD) % decrease*
	1	2	3	4	5	
Angina						
Heparin infusion	28	27	2	2	1	94 (2·1)
Heparin bolus	22	29	19	18	24	30 (11·1)
Aspirin	18	22	17	19	18	18 (4·5)
Silent ischaemic episodes						
Heparin infusion	62	63	20	18	17	71 (2·4)
Heparin bolus	56	56	45	46	45	19 (1·1)
Aspirin	61	54	46	46	49	13 (3·2)
Total ischaemic episodes						
Heparin infusion	90	90	22	20	18	78 (2·2)
Heparin bolus	78	85	64	64	69	23 (3·4)
Aspirin	79	76	63	65	67	15 (2·6)
Total duration ischaemia (min)						
Heparin infusion	1135	1061	178	245	193	81 (3·3)
Heparin bolus	876	968	750	698	779	23 (4·3)
Aspirin	829	881	732	754	776	14 (2·5)

*Compared with day 2

treatment period ($p < 0.0001$). The decrease after intermittent heparin was less (7·0 [2·25] *vs* 5·2 [1·86], $p < 0.0001$). TxA_2 production by platelets was unchanged after heparin infusion (184·1 [53·1] *vs* 181·9 [54·7] ng TxB_2 per 10^8 platelets). Aspirin treatment inhibited TxA_2 production by 97 (2·8)%. After stopping monitoring 17 patients had anginal episodes again.

Heparin infusion or alteplase

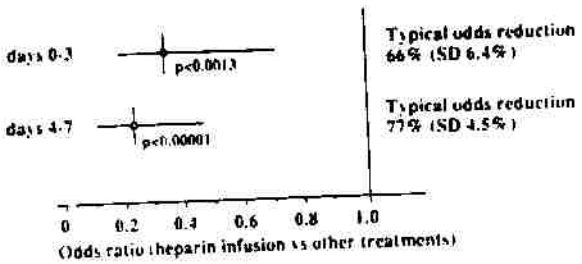
Before treatment the two groups were similar (table IV). As in the first group of patients infused with heparin, heparin infusion in this second group decreased the number of original attacks and the number and duration of ischaemic episodes significantly ($p < 0.001$). Alteplase only slightly affected these variables. The number of anginal attacks was reduced by alteplase on the infusion day only (not significant). On days 4–5, the number of anginal attacks returned to baseline values. After the end of continuous monitoring angina occurred in 19 patients after receiving alteplase compared with 5 in the heparin group.

FPA levels increased significantly immediately after thrombolysis with alteplase (from 6·46 [1·95] to 8·26 [2·25] ng/ml at 6 h, $p < 0.0001$), but returned to baseline on the following days. Fibrinogen levels decreased significantly (from 294·6 [131·7] to 174·0 [45·2] and 186·8 [48·2] mg/dl, after 6 and 12 hours, respectively; $p < 0.0001$). FDP

TABLE IV—RESPONSE TO HEPARIN INFUSION OR ALTEPLASE

	Run-in days		Treatment days*			Mean (SD) % decrease
	1	2	3	4	5	
Angina						
Heparin	28	36	12	5	0	84 (16·7)
Alteplase	21	23	9	19	29	17 (43·4)
Silent ischaemic episodes						
Heparin	54	50	13	14	8	77 (6·4)
Alteplase	51	73	71	47	36	30 (24·5)
Total ischaemic episodes						
Heparin	82	86	25	19	8	80 (10·0)
Alteplase	72	96	80	66	65	27 (8·7)
Total duration of ischaemia (min)						
Heparin	903	1076	253	148	46	86 (9·6)
Alteplase	943	1201	1206	831	746	23 (20·4)

*Heparin infused on days 3–5, alteplase infused for first 12 h of day 3



Odds ratio for heparin infusion versus other treatments for recurrence of angina.

Odds ratio of unity = no treatment effect. Horizontal line = 95% CI

increased from 8·2 [4·4] to 192·0 [155·1] and 83·2 [39·4] ng·ml, after 6 and 12 hours, respectively; $p < 0.0001$). TxA_2 production by platelets was not affected.

The relative risk of therapeutic failure (recurrence of angina) was significantly lower for heparin infusion for the first 3 days and the final 4 days of treatment (figure).

Other events

During the 7 days after the start of treatment, there was 1 non-fatal infarction in the aspirin group and 1 death from infarction in the alteplase group. At the 1 month follow-up visit 3 additional myocardial infarctions were recorded and 2 patients had died. 27 patients underwent coronary artery bypass graft and 17 underwent PTCA (approximately equal numbers in each group). Abnormal coronary anatomy and the occurrence of symptomatic or silent myocardial ischaemia were the main indications for myocardial revascularisation.

Side-effects

During the 7 days haemorrhagic complications and side-effects were limited. No serious bleeding was observed with heparin either in continuous infusion or in bolus; in 2 patients small ecchymoses were noted. 3 patients who received alteplase had painful spontaneous ecchymoses (in 1 patient on the abdomen and in 2 on the thighs) and in 11 other patients negligible bleeding at the injection site occurred. Blood transfusions were never required.

Discussion

Heparin administered by continuous intravenous infusion decreased the number of anginal attacks and silent ischaemic episodes, and reduced the overall daily duration of ischaemia in patients with unstable refractory angina. The efficacy of heparin infusion was supported by the large number of events, even if the number of randomised patients was limited. Intermittent heparin was significantly less effective than the same heparin dosage by continuous infusion, probably because of the irregular plasma levels of heparin.[20,21] The limited decrease in plasma FPA concentration after bolus heparin reflected a low degree of anticoagulation and insufficient inhibition of thrombin generation.

Aspirin did not significantly affect the number or duration of ischaemic episodes despite almost complete inhibition of platelet TxA_2 production. The ineffectiveness of aspirin on myocardial ischaemia indicated that thrombin generation rather than platelets has a primary role in the maintenance of ischaemia in unstable angina.

TABLE I—ENROLMENT

—	No
Admitted with unstable angina	474
Excluded before run-in	75*
Excluded during run-in	302†
Included	97

*Aged over 75 (10), recent gastrointestinal (7) or genitourinary (6) bleeding, stroke within previous 6 months (11), myocardial infarction in previous 3 weeks (10), uncontrolled severe hypertension (11), oral anticoagulant therapy (8), recent surgery/trauma (3), contraindications to aspirin or heparin (9).
†Few ischaemic episodes (295), myocardial infarction (7).

TABLE II—PATIENTS WHO ENTERED RUN-IN PERIOD

—	Initial protocol			Modified protocol	
	Heparin infusion (n = 21)	Heparin bolus (n = 18)	Aspirin (n = 19)	Heparin infusion (n = 19)	Alteplase (n = 20)
Age SD yr	64·9 16·5	62·6 15·3	66·6 15·4	63·9 14·5	62·7 14·6
M F	13	10	13	12	12
Previous angina					
Previous myocardial infarction	9	8	9	5	10

60 mg or more, nifedipine 40 mg or more, and if not contraindicated, metoprolol 100 mg or more, all doses per day. Other medications were administered when needed. Any pre-randomisation treatment was continued throughout the study. If chest pain persisted or recurred nitrates were given sublingually or nitroglycerin was infused.

75 patients did not start the run-in period (table I); 399 patients entered the run-in after having given informed consent. At the end of the run-in period only those patients who had had at least 3 ischaemic episodes or 1 anginal attack lasting 20 or more min during the previous 24 h were defined as having refractory angina and entered into the study. Thus 97 (24%) patients were randomised (table II). The patients' characteristics were similar between groups, including history of coronary surgery and angioplasty, hypertension, diabetes, and smoking, the results of coronary angiography, and cholesterol levels.

Study design and treatment

The run-in period was 2 days, the observation period was up to 7 days, and follow-up was for up to a month. The study was double-blind. The initial protocol allowed for randomisation into three treatment groups: heparin infusion, heparin by repeated bolus, or aspirin. After alteplase (Boehringer Ingelheim) became available, the protocol was modified such that, after breaking the codes, the most effective treatment in the initial phase was compared with alteplase. Placebo was not used because of the patients' conditions and because myocardial ischaemia was objectively assessed by continuous monitoring.

Heparin and aspirin were administered for 7 days to patients who did not leave the study. Heparin was infused intravenously: priming dose 5000 IU followed by 1000 IU/h, and the dose was adjusted to maintain a partial thromboplastin time (PTT) 1·5–2 times baseline. Heparin was given intermittently by injecting 6000 IU every 6 h; patients weighing below 50 kg received 5000 IU. In patients treated with bolus heparin PTT was checked once daily 1 h before next administration to avoid overdose. If PTT was greater than 1·5 times baseline, heparin administration (which was regulated by the head of the haemostasis laboratory who knew the treatment codes) was delayed. Buffered aspirin was administered orally at 325 mg per day. Alteplase was administered by infusion over 12 h to a total 1·75 mg/kg; 0·75 mg/kg was infused during the first hour, 0·5 mg/kg over the next 4 h, and 0·5 mg/kg during the final 7 h. Every patient's drug package contained the active drug and suitable dummy preparations.

Assessments

Myocardial ischaemia was detected by Holter monitoring, which was done during run-in and on days 1–3 of treatment. Only progressive ST segment displacements (≥0·1 mV) lasting at least 60 s were considered evidence of anginal attacks and silent ischaemic episodes. Myocardial infarction was diagnosed on the basis of typical chest pain unrelieved by nitroglycerin and lasting 30 min or more with new ST-T changes or Q-waves[12] and new doubling of baseline levels of creatinine kinase with abnormal MB levels.

During the first 3 days of the treatment period the number of silent ischaemic episodes and anginal attacks and the overall duration of ischaemia per day were recorded. On days 4–7 the number of documented anginal attacks after stopping continuous monitoring was recorded. Patients withdrew from the study if they had an angina attack after the end of continuous monitoring. Withdrawn patients were then treated with the medication judged most suitable by the medical staff.

Patients were followed up for up to a month after randomisation and the number of infarctions, deaths, and coronary artery bypass grafting and percutaneous transluminal coronary angioplasty (PTCA) procedures were recorded. All patients had coronary angiography[13] and lesions were assessed.[14]

Bleeding complications were monitored clinically and by serial measurement of haemoglobin and haematocrit. Severe bleeding was classified as intracranial haemorrhages or haemorrhages leading to a decrease in haematocrit of 10% or more.

Blood samples were obtained immediately before starting treatment and, usually, 6 and 12 h thereafter, and then once daily throughout the study (7 days). We assayed: PTT ('Pathromtin', Behringwerke), fibrinogen ('Multifibren', Behringwerke), fibrinogen degradation product (FDP, 'Thrombo-Wellcotest', Wellcome), and fibrinopeptide A (FPA; ELISA, Boehringer).[15,16] The coefficients of variation for the FPA assay were (intra) 5·9% and (inter) 7·8%. Platelet thromboxane A_2 (TxA_2) production was assayed as TxB_2 (New England Nuclear)[17] in platelet-rich plasma stimulated with 5 NIH U/ml thrombin.[18]

Statistics

We used analysis of variance for repeated measures with a split-plot design for differences between days. For within-day comparisons we used one-way analysis of variance after we had assessed the homogeneity of variances by Levine's test.[19] Multiple comparisons among treatment groups were done with Tukey's test. Relative risk (odds ratio) of treatment failure was evaluated by the Mantel-Haenszel method. The proportion of patients in whom angina recurred was compared by Fisher's exact and χ^2 tests. Results are expressed as mean (SD).

Results

Heparin infusion, heparin bolus, or aspirin

During the run-in period (days 1–2) the groups were similar clinically (table III). After infusion of heparin there were significant decreases in the number of anginal attacks and of silent and total ischaemic episodes, and in the total duration of ischaemia compared with the other two groups ($p < 0·001$). Within the group infused with heparin, the decreases in these variables were significant compared with the run-in days ($p < 0·001$). The decrease in ischaemic episodes was significant by day 3 (ie, the first day of treatment) in this group. After continuous monitoring was stopped anginal attacks recurred in only 4 of 21 patients during the subsequent 4 days of treatment (days 6–9). Angina recurred on these days in all patients who received bolus heparin and in 17 of 19 patients who received aspirin ($p < 0·0001$ between groups).

Plasma FPA levels also decreased from 6·8 (2·23) ng ml during the run-in period to 3·0 (0·97) ng ml during the

Alteplase tended to decrease the frequency of angina on the day of infusion only, but was ineffective in lowering the number or overall duration of ischaemic episodes. The same preparation of alteplase at the same dosage has been shown to increase coronary patency and induce a temporary clinical improvement.[4] However, in that study, full heparin anticoagulation was also included so the real efficacy of thrombolytic therapy per se could not be established. In other uncontrolled studies of small numbers of patients,[2,3,6-22] thrombolytic treatment with intermittent heparin produced limited and erratic clinical improvement that was not usually associated with consistent changes in angiographic coronary stenoses. Thus, thrombolytic therapy in unstable angina is probably indicated in special conditions[23] and appears to be effective only if given with full anticoagulation.[4] However, such co-administration does not seem to confer advantages over heparin infusion alone, whereas the haemorrhagic risks are higher.

The effectiveness of heparin and the lack of efficacy of alteplase suggest that the acute effect of heparin is not attributable to its activity on intracoronary thrombus growth but rather to the inhibition of thrombin formation. Necropsy[24] and angioscopic observations[25,26] have shown that refractory unstable angina is often associated with plaque fissuring or ulceration, which can easily trigger local formation of thrombin sufficient to cause vascular contraction in the absence of endothelium.[27,28]

Our results indicate that the role of thrombin activation in the pathogenesis of unstable angina is important compared with platelet aggregation. Clinically heparin by continuous infusion is a prompt, effective, and safe treatment for myocardial ischaemia in unstable angina refractory to conventional treatments.

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From The Lancet

The African kola nut

At a meeting of the Balloon Society, held at St. James's Hall, Mr T. Christy read a paper on the uses of the kola nut. It is well known this fruit has long been in use amongst the natives of Western Africa when on long and tedious marches, as it is said to possess great sustaining and stimulating powers. Travellers declare that not only does this nut reinforce the system when it is debilitated by fatigue, but that it also quiets temporarily the pangs of hunger and thirst; and, in fact, the natives frequently carry powdered kola in lieu of provisions. Analysis has shown that it contains 2·5% of caffeine, with very little tannin (about 1·5%), being much better in this respect, therefore, than tea, which usually contains at most 2·5% of the alkaloid, with 16 or 17% of tannin. At about the same time a communication from Dr Heckel of Marseilles was read at the Paris Academy of Medicine on the same subject, in which the writer suggests that powdered kola nut should be used as part of the soldiers' rations as a preventive of fatigue on long marches. He mentions a test made during the manoeuvres of the Sixth Army Corps, among other instances, in support of his statement. From these facts there seems every chance of kola becoming in course of time a powerful rival of tea and coffee, as well as a substitute for so-called "pick-me-ups.".

(From *The Lancet* of 10 May 1890)