# Randomised comparison of subcutaneous heparin, intravenous heparin, and aspirin in unstable angina. Studio Epoorine

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## Summary

Intravenous heparin has been used in the control of myocardial ischaemia in patients with unstable angina. We set out to assess the efficacy of subcutaneous heparin in reducing myocardial ischaemia in patients with unstable angina.

343 of 399 patients with unstable angina were monitored for 24 h and 108 were refractory to conventional antianginal treatment and were entered into a randomised multicentre trial. 37 patients were assigned to heparin infusion (partial thromboplastin time 1·5–2 times baseline), 35 to subcutaneous heparin (adjusted dose with partial thromboplastin time 1·5–2 times baseline), and 36 to aspirin (325 mg daily). All had additional conventional antianginal therapy. After the run-in patients were monitored for 3 days. The primary endpoint was reduced myocardial ischaemia assessed by the number of anginal attacks, silent ischaemic episodes, and duration of ischaemia per day. At 1 week and 1 month we accounted for anginal attacks and other clinical events (myocardial infarction, revascularisation procedures, and death). Aspirin did not significantly affect the incidence of myocardial ischaemia. On the first 3 days, infused and subcutaneous heparin significantly decreased the frequency of angina (on average by 91% and 86%, respectively), episodes of silent ischaemia (by 56% and 46%), and the overall duration of ischaemia (66% and 61%) versus run-in day and aspirin ($p<0·001$ for all variables).

The favourable effects of heparin therapy remained evident during follow-up. Only minor bleeding complications occurred. Subcutaneous heparin is effective in the control of myocardial ischaemia in patients with unstable angina.

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## Introduction

Intravenous heparin is a highly effective treatment for the control of myocardial ischaemia in patients with unstable angina.[1,2] Continuous intravenous heparin infusion is not always easily feasible in small country hospitals or in patients treated at home because this treatment requires pumps and careful monitoring of blood clotting by partial thromboplastin time (PTT). Subcutaneous administration of heparin is easy, does not require pumps, and, if appropriately done, gives the same anticoagulant effect (PTT values within effective range) as heparin infusion.[3] In the treatment of venous thromboembolism subcutaneous heparin can be as effective as heparin infusion and has a lower frequency of bleeding.[3,4] Subcutaneous heparin given at low doses prevented the recurrence of angina in patients discharged from hospital[5] and can be used for medium-term and long-term treatment.[6,7] We set out to assess the effectiveness of subcutaneous heparin, heparin infusion, and aspirin on myocardial ischaemia in patients with refractory unstable angina.

## Patients and methods

### *Patients*

Patients were admitted if they had unstable angina—typical chest pain occurring at rest or on minimum effort with reversible ST segment elevation or depression of at least 0·1 mV 80 ms after the J point, or a single episode of chest pain lasting 20 min or longer with serum concentration of creatine kinase less than twice the upper limit of normal. All patients had had a painful episode within 24 h of admission. Table 1 shows exclusion criteria. All patients were treated orally with buffered aspirin 325 mg per day, isosorbide dinitrate 40 mg per day or more, nifedipine 40 mg per day or more, and, if not contraindicated, metoprolol 200 mg per day. Other platelet-active drugs, non-steroid anti-inflammatory drugs, oral anticoagulants, digoxin, and antidepressant drugs were excluded. Other medications, such as diuretics or antihypertensives, were given if needed. We

| | |
|---|---|
| **General characteristics** | |
| Admitted for unstable angina | 399 |
| Excluded before entering the run-in | 56 |
| Submitted to the run-in period | 343 |
| Excluded during the run-in | 238 |
| Enrolled | 108 |
| **Reasons for exclusion before the run-in period** | |
| Age >70 | 12 |
| History of stroke within 6 months | 5 |
| Recent myocardial infarction (within 6 weeks) | 7 |
| Uncontrolled severe hypertension | 16 |
| Recent surgery or trauma | 6 |
| Contraindications to aspirin or heparin | 10 |
| **Reasons for exclusion during the run-in period** | |
| Low number of ischaemic episodes | 230 |
| Occurrence of myocardial infarction (Q-wave and no Q-wave) | 5 |

Table 1: **Characteristics of trial patients**

| | Heparin infusion | Subcutaneous heparin | Aspirin |
|---|---|---|---|
| **Patient characteristics** | | | |
| Total patients | 37 | 35 | 36 |
| Mean (SD) age (years) | 64 (9) | 62 (6) | 66 (6) |
| Sex (M/F) | 25/12 | 21/14 | 23/13 |
| Previous angina | 23 | 19 | 24 |
| Previous myocardial infarction | 15 | 15 | 17 |
| Previous coronary surgery | 0 | 0 | 0 |
| Hypertension | 8 | 7 | 8 |
| Diabetes | 7 | 8 | 7 |
| Cigarette smokers | 24 | 19 | 28 |
| Mean (SD) cholesterol (mmol/L) | 7·1 (1·1) | 6·9 (1·4) | 7·3 (1·2) |
| Mean (SD) high-density lipoprotein cholesterol (mmol/L) | 1·3 (0·3) | 1·2 (0·2) | 1·2 (0·2) |
| **Coronary angiography** | | | |
| Normal coronary angiography | 0 | 0 | 0 |
| Coronary artery diameter reduction | 4 | 3 | 3 |
| Left main >50% | 12 | 17 | 17 |
| Proximal anterior descending >70% | 16 | 9 | 14 |
| Left circumflex >70% | 16 | 9 | 14 |
| Right >70% | 12 | 17 | 19 |
| Ejection fraction (%) | | | |
| >50 | 23 | 24 | 25 |
| 40–50 | 9 | 8 | 9 |
| <40 | 5 | 3 | 2 |

Table 2: **Demographic, clinical and angiographic characteristics of the study groups**

| | Run-in day | | Treatment days | | Mean (SD) decrease | |
|---|---|---|---|---|---|---|
| | Day 1 | Day 2 | Day 3 | Day 4 | % | p |
| **Anginal attacks (episodes per day)** | | | | | | |
| Heparin infusion (n=37) | 22 | 1† | 3† | 2† | 91 (4) | <0·001 |
| Subcutaneous heparin (n=35) | 22 | 5* | 2† | 2† | 86 (6) | <0·001 |
| Aspirin (n=36) | 24 | 19 | 18 | 15 | 28 (7) | NS |
| **Silent ischaemic episodes (episodes per day)** | | | | | | |
| Heparin infusion | 81 | 52* | 32† | 24† | 56 (14) | <0·001 |
| Subcutaneous heparin | 74 | 52 | 38† | 29† | 46 (13) | <0·001 |
| Aspirin | 79 | 79 | 75 | 78 | 2 (2) | NS |
| **Total ischaemic episodes (episodes per day)** | | | | | | |
| Heparin infusion | 103 | 53† | 35† | 26† | 63 (11) | <0·001 |
| Subcutaneous heparin | 96 | 57† | 40† | 31† | 56 (11) | <0·001 |
| Aspirin | 103 | 98 | 93 | 93 | 8 (2) | NS |
| **Duration (min ischaemia per day)** | | | | | | |
| Heparin infusion | 1080 | 557† | 356† | 188† | 66 (14) | <0·001 |
| Subcutaneous heparin | 1151 | 641† | 394† | 313† | 61 (12) | <0·001 |
| Aspirin | 1044 | 1067 | 879 | 991 | 6 (7) | NS |

*vs* run-in day: *p<0·01, †p<0·005. NS=not significnat.

Table 3: **Ischaemic episodes and overall duration of myocardial ischaemia during the monitoring period**

continued prerandomisation treatments throughout. If chest pain persisted or recurred, nitrates were given sublingually or nitroglycerin was infused intravenously. After 1 day on anti-anginal treatment, patients entered the 24 h run-in period during which Holter monitoring was done.

399 eligible patients were admitted with unstable angina: 56 did not start the run-in period (table 1) and 343 patients were admitted after giving their informed consent. At the end of the run-in period only those patients who had had at least three ischaemic episodes during the Holter monitoring period or one documented anginal attack were admitted to the trial and were randomised. Thus 108 (26%) patients were randomised (table 1). The patients of all groups had similar features (table 2).

### *Study design, end-point, and treatment*

The study was a prospective, randomised, multicentre trial. After the 1 day run-in period, patients were randomised into three treatment groups. We continued trial therapy for 3 days and continuously monitored electrocardiographic (ECG) measurements. Follow-up was for 1 month. After this 3-day treatment, the dose of study treatment was left to the discretion of the medical staff who could either discontinue or modify the dose but could not change the antianginal therapy. Data were collected at the end of the 3 monitoring days and thereafter 1 week and 1 month after randomisation.

The primary end-point was reduced myocardial ischaemia as seen by the number of anginal attacks, the total number of ischaemic episodes (anginal attacks plus silent ischaemic episodes), and overall duration of ischaemia (minutes per day) during the 3 days of Holter monitoring. Patients were followed up for a month after randomisation, and the recurrence of angina (defined as recurrent chest pain at rest with ischaemic ECG ST-T segment changes occurring despite maximal antianginal therapy), myocardial infarction, deaths, and coronary revascularisation procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) were also recorded.

Patients were randomly allocated to one of three treatment groups: heparin infusion, subcutaneous heparin, or aspirin. Aspirin administration was withheld in the two heparin treatment groups but was recommended if heparin was discontinued.

Heparin was infused intravenously, with a priming dose of 5000 IU followed by 1000 IU per h, and the dose was adjusted to maintain the PTT between 1·5 and 2 times the baseline. The PTT was assessed twice a day (at 8 am and 6 pm). In a preliminary investigation we identified the most appropriate subcutaneous heparin dose according to body weight and sex. Subcutaneous heparin (Calciparina, Italfarmaco, Milan, Italy) was administered every 8 h. Male patients weighing above 65 kg received 10 000 IU; male patients less than 65 kg were given 7500 IU. Female patients received 7500 IU if they weighed between 65 kg and 90 kg, 10 000 IU if they weighed more than 90 kg, or 5000 IU if they weighed less than 65 kg. In all patients the first subcutaneous dose was given simultaneously with an intravenous priming dose of 5000 IU. The PTT was assessed before starting heparin treatment and every day 2 h before the afternoon injection. If the PTT value was more than twice the baseline, the next heparin treatment was postponed for 3 h. If the PTT value was less than 1·5 times the baseline, the next heparin administration was brought forward by 2 h and further injections were reset at 8 h intervals. The algorithm of heparin administration was regulated by the physicians of the clinical centres. Buffered aspirin was given orally at 325 mg per day.

### *Assessments*

Myocardial ischaemia was detected by Holter monitoring, which was done during the run-in period and the following 3 days of treatment. Only progressive ST segment shifts (≥0·1 mV) lasting at least 60 s were used as evidence of myocardial ischaemia. Myocardial infarction was diagnosed on the basis of typical chest pain unrelieved by nitroglycerin with new ST-T changes or Q-waves[8] and new doubling of creatine phosphokinase (CK) baseline levels with MB isoenzymes above 10%.

During the first 3 days of treatment we recorded anginal attacks, silent ischaemic episodes, and overall duration of ischaemia per day. Each Holter recording was immediately read blind of treatment by physicians of the clinical centre participating in the study. All Holter recordings were sent to the coordinating centre for reviewing and final evaluation by three blinded observers.

On days 4–7 the number of documented anginal attacks after stopping continuous monitoring was recorded. After the first week the number of anginal attacks was recorded weekly up to 1 month. Myocardial infarction, death, and revascularisation procedures were also recorded.

All patients had coronary angiography.[9,10] Bleeding complications were monitored clinically and by serial measurement of haemoglobin and haematocrit. Severe bleeding was classified as intracranial haemorrhage or haemorrhages leading to a decrease of 10% or more in haematocrit.

### Statistical analysis

From the data obtained previously by our group[1] we expected a cumulative rate of three ischaemic episodes per day and 30 min of ischaemia per day during the run-in period, with an overall reduction of 15% for both variables in the aspirin group. To detect a 50% reduction in the event rate of heparin-treated groups, each group needed at least 35 patients. End-point analysis was done by an independent biostatistical centre after enrolment was completed.

We analysed events according to intention to treat. A secondary analysis was also done by censoring the events at the time when a patient was withdrawn from trial therapy (efficacy analysis).

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 with Levine's test.[11] Multiple comparisons among treatment groups were made with Tukey's test. The proportion of patients in whom angina recurred was compared by Fisher's exact and $\chi^2$ tests. Results are expressed as mean (SD). A p value less than 0·05 was taken as statistically significant.

## Results

### Myocardial ischaemia

108 patients were randomised, 37 to heparin infusion, 35 to subcutaneous heparin, and 36 to aspirin. During the run-in period (day 1) the groups were homogeneous for the number of anginal attacks, silent ischaemic episodes, and for total duration of ischaemia (table 3).

Aspirin did not significantly affect the number of anginal attacks, total ischaemic episodes, or the duration of ischaemic episodes (−28%, −8%, and −6%, not significant for all variables) (table 3). By contrast, heparin infusion and subcutaneous heparin induced a significant decrease in the number of anginal attacks (−91% and −86%), silent ischaemic episodes (−56%, −46%), and in the total duration of ischaemia (−66%, −61%) compared with the run-in period ($p<0·001$). Both treatments differed in the three measures from the aspirin group ($p<0·05$, $p<0·001$, $p<0·001$ for both treatments) (table 3).

In both heparin treatment groups myocardial ischaemia was easily controlled because the number of anginal attacks and total ischaemic episodes and the duration of ischaemia decreased already during the first 24 h (table 3).

### Anginal attacks and other events during follow-up

When we stopped continuous Holter monitoring, 24 patients (65%) remained on heparin infusion, 27 (77%) on subcutaneous heparin, and 28 (78%) on aspirin for 4 extra days. Analysis by intention to treat that limited exposure to these 4 days, showed significant advantages for heparin treatments (heparin infusion and subcutaneous heparin) compared with aspirin: 22 of 36 patients (61%) assigned to aspirin experienced anginal attacks versus 6 of 37 (16%) given heparin infusion and 5 of 35 (14%) given subcutaneous heparin ($\chi^2=23·792$, $p<0·001$). Anginal episodes occurred more frequently in patients who discontinued the heparin treatments (4 of 13 [30%] for heparin infusion and 2 of 8 [25%] for subcutaneous heparin) than in those who remained on heparin (2 of 24 [8%] for heparin infusion and 3 of 27 [11%] for subcutaneous heparin). However, these differences did not reach statistical significance ($\chi^2=1·691$, $p=0·193$ and $\chi^2=0·169$, $p=0·681$, respectively).

| | Heparin infusion (n=37) | Subcutaneous heparin (n=35) | Aspirin (n=36) |
|---|---|---|---|
| Myocardial infarction | 0 | 2 | 2 |
| Death | 2 | 1 | 2 |
| Bypass | 11 | 6 | 11 |
| Coronary angioplasty | 4 | 5 | 5 |

Table 4: **Clinical events occurring within 1 month of randomisation**

In the next 3 weeks, all patients on heparin infusion and 12 out of the 35 on subcutaneous heparin stopped the treatment, whereas the other 23 patients of this group were treated with 12·5 U daily. Angina recurrence was more frequent in patients who stopped subcutaneous heparin (6 of 12, 50%) than in those who remained on heparin treatment (3 of 23, 13%) ($\chi^2=3·870$, $p<0·49$). Aspirin treatment was continued in 25 patients and its discontinuation did not modify angina frequency. In fact, 5 of 11 patients who discontinued aspirin and 14 of 25 patients who remained on aspirin had angina ($\chi^2=0·049$, $p=0·825$). Angina recurred more frequently in patients on aspirin (14 of 25, 56%) than in those on subcutaneous heparin (3 of 23, 13%) ($\chi^2=7·877$, $p<0·005$). At 1 month follow-up the distribution of events did not differ among the three groups (table 4).

### Side-effects

Minor bleeding events (epistaxis or small ecchymoses) were seen in 2 patients treated with aspirin and in 2 patients treated with intravenous heparin.

## Discussion

These results show that subcutaneous heparin is effective in the control of myocardial ischaemia. Heparin treatments by intravenous infusion and subcutaneous administration decreased the number of anginal attacks and silent ischaemic episodes and reduced the overall daily duration of ischaemia in patients with refractory unstable angina. The efficacy of the two heparin treatments was supported by the large number of events, even if the number of randomised patients was limited. The favourable effect of heparin treatment was prompt because it significantly reduced the anginal attacks and the duration of ischaemia after the first 24 h. Since all patients received aspirin during the run-in period, we cannot exclude a crossover effect of aspirin in the efficacy of heparin treatments. However, the effect of aspirin was unlikely to have influenced the results because the efficacy of heparin progressively increased during the study whereas aspirin remained ineffective. From the intention-to-treat analysis the benefit obtained from heparin treatment during the 3 monitoring days was still present at the end of the first week of observation. The differences in recurrence of angina between patients who discontinued and patients who remained on heparin treatment were not statistically significant. However, our results agree with those of Theroux et al[12] who found a rebound of clinical symptoms after heparin discontinuation. Importantly, our results suggest that continuation of heparin treatment for at least 4 weeks may be useful in patients with unstable angina: during this time subcutaneous heparin prevented recurrence of angina whereas aspirin did not.

Although aspirin given during the run-in day to the patients of the three groups may have contributed to the favourable effect of heparin, our results suggest that by

itself aspirin could not affect myocardial ischaemia in unstable angina. The ineffectiveness of aspirin in the control of myocardial ischaemia as opposed to the prevention of vascular events may have a dual cause: the lack of effect on thrombin-induced platelet aggregation and the fact that thromboxane A2 is generally produced by monocytes within the vessel wall itself,[13] which aspirin is unable to reach in active form because of its rapid hydrolysis by esterases.[14] Aspirin might be expected to halt the process of platelet aggregation, one of the factors responsible for myocardial infarction complicating unstable angina.[15,16] However, heparin infusion prevented myocardial infarction more efficiently than aspirin during the acute phase of unstable angina.[2] Likewise, a combination of aspirin plus anticoagulant seems to work better than aspirin alone in reducing the incidence of total ischaemic events in patients with unstable angina.[17] The results from these studies and from the present investigation thus confirm the prominent role of increased thrombin formation in myocardial ischaemia occurrence in patients with unstable angina.[1,13]

Appropriate doses of subcutaneous heparin give a prompt, safe treatment that is as effective as heparin infusion for the control of myocardial ischaemia in patients with unstable angina refractory to conventional antianginal therapy.

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