Enhanced thrombolytic efficacy and reduction of infarct size by simultaneous infusion of streptokinase and heparin

Giovanni Melandri, Angelo Branzi, Franco Semprini, Vittorio Cervi, Nazzareno Galié, Bruno Magnani

Abstract
Because paradoxal increase in thrombin activity was reported after the administration of streptokinase in patients with acute myocardial infarction the velocity of reperfusion and degree of myocardial damage were studied when heparin was infused during rather than after streptokinase infusion. Thirty-seven consecutive patients with acute myocardial infarction were randomized to receive intravenous heparin during (group 1, n = 18) or after (group 2, n = 19) streptokinase (1.5 megauits over 60 minutes). Markers of reperfusion were monitored every 15 minutes for 3 hours. The serum concentration of creatine kinase was measured every 2 hours. The two groups were similar in terms of age and sex distribution, infarct site, time to treatment, and baseline myocardial ischaemia. Patients in group 1 had a significantly shorter mean (SD) reperfusion time (57 (35) minutes v 101 (47)). From 60 to 120 minutes after randomisation there were significant differences in ST segment elevation between the groups. Serum creatine kinase MB peak earlier (8 (2) hours) in group 1 than in group 2 (10 (4) hours). The peak concentration was significantly lower in group 1 (87 (47) mU/ml) than in group 2 (134 (96) mU/ml) and infarcts were smaller (25-2 (9-8) gram equivalents/m^2) in group 1 than in group 2 (35-1 (10-2) gram equivalents/m^2).

Simultaneous infusion of heparin and streptokinase speeds up the appearance of signs of reperfusion and reduces infarct size.

The role of heparin in the treatment of acute myocardial infarction by thrombolysis is still controversial. Some recommend intravenous heparin from the start of thrombolytic treatment, and others immediately or 2-6 hours after the infusion of the thrombolytic agent. Recent large clinical trials of thrombolytic treatment in acute myocardial infarction considered heparin as an option. Thrombin concentration increased in acute myocardial infarction and again paradoxically after streptokinase or urokinase was given.

We studied the thrombolytic efficacy of a simultaneous infusion of streptokinase and heparin in patients with acute myocardial infarction.

Patients and methods
PATIENTS
Patients with >30 min of ischaemic chest pain (unrelieved by sublingual glyceryl trinitrate) and ST segment elevation (>0.1 mV in two or more standard frontal plane leads or >0.2 mV in two or more precordial leads) were eligible for the study. Patients were not eligible if more than 3 hours had elapsed since the onset of chest pain. Additional exclusion factors were age >70 years, uncontrolled hypertension (diastolic pressure >110 mm Hg; systolic pressure >200 mm Hg), a cerebrovascular accident within the past 3 months, known haemorrhagic diathesis or active haemorrhage, an important surgical procedure within the past 2 months, previous coronary artery bypass grafting, prolonged cardiopulmonary resuscitation, oral anticoagulant treatment, child-bearing age in women, or serious advanced illness.

TREATMENT PROTOCOL
All patients received an intravenous infusion of streptokinase (1.5 megauits over 1 h). Each patient was randomly assigned to receive either a simultaneous infusion of heparin (aiming at an activated partial thromboplastin time of 2-0 to 2-5 times normal) (group 1) or saline (group 2). At the end of streptokinase infusion group 2 patients were given heparin (according to the same protocol as group 1). Intravenous heparin was continued for 4-5 days provided that there was no serious bleeding. Subsequently patients were placed on an antiplatelet regimen consisting of aspirin (400 mg per day) and dipyridamole (75 mg three times per day). During the first 24-48 h patients were also given intravenous glyceryl trinitrate to unload the heart and reduce coronary vasomotion. Other medications were prescribed in accordance with the individual’s clinical condition.

ASSESSMENT OF REPERFUSION
Before the start of thrombolysis 12 lead electrocardiograms were obtained on a Hewlett Packard cardigraph 4700 A. The amount of myocardium at risk was estimated by the method of Hogg et al. The ST segment area was calculated for each lead showing ST elevation and measured as the area above the isoelectric line from the J point to the end of the T
wave. The sum of scores for all leads provided an index of myocardial ischaemia. Patients
were asked to grade the intensity of chest pain from 0 to 100 on a visual analogue scale. Then
the 12 lead electrocardiograms and the intensity of chest pain were monitored every 15 min
for 3 hours and also whenever there was a change in symptoms, ST segment shift on the
monitor, or in cardiac rhythm. Blood samples were drawn to measure serum creatine kinase
MB every second hour during the first 16 hours and then every fourth hour for the next 24
hours. Then serum creatine kinase MB was measured once daily until it became normal.

To speed up the initial treatment we chose to
recognise reperfusion non-invasively. Reper-
fusion was considered to have occurred when
there was a gradual reduction in the size of the
ST segment shift to <50% of the basal value
accompanied by a sudden or gradual lessening
of chest pain and a rapid rise in the serum
concentration of creatine kinase MB with a
peak within 13 hours of the onset of chest pain.
The interval to reperfusion (reperfusion time)
was measured from the start of thrombolysis to
the onset of the resolution of the ST segment
elevation. All the electrocardiograms, the
records of the course of chest pain, and the
enzymatic time-activity curves were analysed
by two investigators who were unaware of the
patient’s treatment group. This non-invasive
method has been validated by angiography and
is currently used in clinical trials. Infarct size
was measured according to Sobel et al. Several
experimental and clinical studies showed
that measurement of infarct size by enzyme
tests is feasible and meaningful after
thrombolysis.

STATISTICAL ANALYSIS
All values are expressed as mean (SD). Paired
and unpaired t tests were used to compare the
means of continuous variables. χ² tests (with
Yates’s correction when indicated) were used to
calculate significant differences between the
two treatment groups. This non-invasive
method has been validated by angiography
and is currently used in clinical trials. Infarct
size was measured according to Sobel et al. Several
experimental and clinical studies showed
that measurement of infarct size by enzyme
tests is feasible and meaningful after
thrombolysis.

Results
Thirty-seven patients were randomly allocated
to be treated with streptokinase plus simulta-
neous heparin (n = 18, group 1) or streptokin-
ase followed by heparin (n = 19, group 2).
Baseline characteristics were similar in the two
groups (table). In particular the degree
of ischaemia on the electrocardiogram
at presentation was similar in both groups (the
ST segment area was 112 (62) mm² in group 1
and 120 (58) mm² in group 2; p = NS). Blinded
assessment showed that 17 of the 18
patients in group 1 and 17 of the 19 patients
in group 2 had non-invasive signs of reperfusion.
Reperfusion time was significantly shorter in
group 1 (57 (35) min vs 101 (47) min; p < 0.005)
(fig 1). Figure 2 shows the time course of ST
segment elevation. In most patients there were
no statistically significant differences between
the two groups up to 45 minutes after ran-
donisation. At 60 minutes group 1 patients
showed a significantly lower ST segment eleva-
tion (p < 0.05). The difference remained signif-
ificant up to 120 minutes.

The time to peak creatine kinase MB was 8
(2) h in group 1 and 10 (4) h in group 2
(p < 0.05). On average the peak concentration
of creatine kinase MB was 87 (47) mU/ml in
group 1 and 134 (96) mU/ml in group 2
(p < 0.05). The infarct was significantly
smaller in group 1 (25 (2) g equivalents/m²)
than in group 2 (35 (10) g equivalents/m²)
(p < 0.05).

Many patients developed skin haematomas.
Three patients (16.6%) in group 1 and six
(31.5%) in group 2 had major bleeding com-

Table 1

<table>
<thead>
<tr>
<th>Baseline characteristics of patients in study groups</th>
</tr>
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<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Smoker (%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
</tr>
<tr>
<td>Anterior MI (%)</td>
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<tr>
<td>Inferior MI (%)</td>
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<tr>
<td>Prior MI (%)</td>
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<tr>
<td>Mean (SD) time to treatment (min)</td>
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<td>Mean (SD) ST segment area (mm²)</td>
</tr>
</tbody>
</table>

MI, myocardial infarction.
None of the variables was significantly different in the two
groups.
Acute myocardial infarction is associated with increased thrombin activity. The main effects of thrombin include platelet activation, fibrin formation, and impairment of fibrinolytic activity. Other important effects include the stabilisation of fibrin polymers and disturbance of endotheial cells that results in tissue factor induction and binding of neutrophils. Evidence is now accumulating that the administration of streptokinase leads to an immediate, paradoxical increase in thrombin activity. This effect has several explanations. Firstly, removal of the thrombus may expose the thrombogenic surface of the infarct vessel. Reperfusion of ischaemic myocardium may be associated with a washout of thrombolytic material. Finally, thrombin absorbed on to the fibrin clot may be released by thrombolytic treatment and regain its activity. So there are strong theoretical reasons for giving heparin with streptokinase. But the possibility of bleeding complications has prevented heparin being regarded as mandatory in some strategies should also take account of the speed of resolution of electrocardiographic signs of acute myocardial infarction. The reduction of infarct size that we saw in one patient in group 1 and two in group 2 suggests that heparin with streptokinase. But the possibility of bleeding complications has prevented heparin being regarded as mandatory in some recent large scale clinical trials.

Our study shows that when heparin treatment is given there is a clear advantage in infusing it with rather than after streptokinase. This conclusion is supported by the quicker resolution of electrocardiographic signs of ischaemia and by the earlier peaking of serum concentrations of creatine kinase MB. These signs of faster reperfusion were associated with a significantly lower peak value of serum creatine kinase and a smaller infarct. Earlier studies by our group in which serum creatine kinase MB was measured frequently showed a good correlation between left ventricular function and both enzymatically assessed infarct size and the extension of resting thallium-201 perfusion defects (measured by single-photon emission tomography).

The reduction of infarct size that we saw in the present study when heparin was given early was the result of a mean reduction of 44 minutes in the time to reperfusion. These data confirm that the human heart is very sensitive to the duration of ischaemia before reperfusion and support the concept that reperfusion strategies should also take account of the speed of reperfusion.

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