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Long-Term Anticoagulation with Heparin in Patients Receiving Fibrinolytic Therapy for AMI

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Abstract

Background: The fibrinolytic therapy for acute myocardial infarction fails to achieve reperfusion in 40-70% of patients. We did a trial to compare the 48 and 96 h heparin administration in patients undergoing fibrinolysis by streptokinase for acute myocardial infarction. Methods: 99 patients with acute ST-elevation myocardial infarction were randomly assigned an intravenous 48-h infusion of heparin (n=53) or 96 h (n=46) administration together with a standard 1,5 million unit dose of streptokinase). The primary endpoint was 30-day mortality and re-infarction during 96 h of hospitalization. Findings By 30 days, 5 patients (9,4%) in 48 h heparin group and 4 patients (8,7%) in the 96 h heparin group had died. There were significantly fewer reinfarctions in patients of 96 h heparin group than in 48 h heparin group (t<0,05). Conclusions: Long-term 96 h heparin anticoagulation combined with streptokinase infusion reduced MI mortality by 7,4% in compare with short term 48 h heparin administration and reduced the rate of reinfarction during hospitalization by 18,4%.

Keywords: *heparin, anticoagulation, fibrinolysis, myocardial infarction*

Introduction

Styreptokinase is commonly used in patients with acute myocardial infarction as fibrinolytic therapy[1,2,3]. However, fibrinolysis remains an important trigger for further thrombus formation.

Heparin is a indirect thrombin inhibitor and inhibits mainly fluid-phase thrombin, so it might be expected that the long term heparin administration could reduce more effectively the complications of acute myocardial infarction after fibrinolysis[4,5,6].

We therefore compared the effect on 30-day mortality and hospitalization re-infarction rate after long and short term heaprine administration together with fibrinolysis by streptokinase.

Patients and Methods

Patients of any age were eligible if they presented within 6 h of the onset of chest discomfort lasting more than 30 min and had at least 1 mm of ST elevation in two or more contiguous leads (or at least 2 mm of ST elevation in two contiguous precordial leads in V1 –V3) or presumed new left bundle branch block. The exclusion criteria were: active bleeding or known haemorrhagic diathesis, previous stroke, transient ischaemic attack within 6 months, current warfarin therapy, major surgery or trauma within 6 weeks, recent non-compressible vascular puncture, blood pressure of more than 180/110 mm Hg, low-molecular-weight heparin therapy within 12

h, an activated partial thromboplastin time (APTT) of at least 50 s in patients who had previously received heparin, and previous treatment with streptokinase.

All patients were given 150–325 mg aspirin and randomly assigned to receive an intravenous infusion of heparin either during 48 or 96 hrs following or at the same time with streptokinase. Streptokinase was given as a 1,5 million unit infusion over 30–60 min. Patients assigned heparin were given a bolus of 5000 units followed by an initial infusion of 1000 units/h in patients weighing 80 kg or more, and 800 units/h in those weighing less than 80 kg during 48 and 96 hrs.

The primary endpoint was mortality within 30 days. The major secondary endpoints was the incidence of in-hospital reinfarction.

Reinfarction was defined as ischaemic chest pain lasting 30 min or more with new ST elevation of at least 1 mm, reinfarction occurring after 18 h was defined as a creatine kinase or creatine kinase MB concentration of at least twice the upper limit of the normal range and at least 50% higher than the previous baseline concentration, or new Q waves of 30 ms or more as distinct from the enrolment myocardial infarction.

Results

99 patients were randomised into the trial. The median age of the patients was 57,8 years (50,8–68,9), and 23,4% were women. All other baseline characteristics were well balanced.

The median time from symptom onset to the start of fibrinolytic and antithrombin therapy was 4,3 h in both groups.

The median duration of the heparin infusion short term 48,0 h (48,0–48,5) and long term 96,2 (96,0-96,4). Aspirin was given to 99,0% of pts, and intravenous beta-blockers were given to 12,4% of patients in both groups. The median hospital stay was 5 days (1–8) in both group. There was no evidence of significant heterogeneity of treatment differences across any of the subgroups.

Mortality The number of patients who died by 30 days was less in the long-term heparin group in compare to short-term group (8,7% *vs* 9,4%, p<0,05).

Reinfarction and the composite endpoint of death or reinfarction reduced during hospitalization by 18,4% in group of patients treated by streptokinase with heparin long term in compare to short term infusion.

Among in-hospital reinfarctions 88,0% occurred after 18h and were associated with increased enzyme concentrations in 86%. 24,5% of patients who had a reinfarction died.

Discussion

In this trial of thrombin-specific anticoagulation used in conjunction with streptokinase, long term anticoagulation did reduced overall mortality within 30 days compared with short term infusion of heparin. At the same time, there was evidence that long term infusion reduced the rate of adjudicated reinfarction by 18,4% throughout the hospital stay, validating the role of long term anticoagulation in combination of fubrinolysis in this setting.

So, the mortality point estimate for long term anticoagulation was lower than that for short term heparin administration and the trial shows that long term administration is not inferior to short term infusion.

The reduction in reinfarction is a key finding of this trial, with potentially important implications for clinical practice: fewer coronary-artery thrombi, and consequently a lower rate of reinfarction.

Thus, long term anticoagulation with heparin provides advantages over the short term use of heaparin and monotherapy by streptokinase. The clinical benefit/risk relation for long term use versus short term has shown a reduced risk of reinfarction and suggests a lower risk of the combined outcome of death and reinfarction.

	Heparin + streptokinase group (n=53)	Streptokinase group (n=46)
Demographics		
Median age (years)	57,8 (51,1–68,5)	57,9 (50,2–69,3)
Number >65 years	11 (20,7%)	12 (26,0%)
Number of women	9 (16,9%)	8 (17,4%)
Risk factors		
Smoking history:		
Never smoked	12 (22,6%)	9 (19,5%)
Past smoker	26 (49,0%)	16 (34,7%)
Current smoker	21 (39,6%)	21 (45,6%)
Hypertension	29 (54,7%)	23 (50,0%)
Hypercholesterolaemia	15 (28,3%)	12 (26,1%)
Diabetes	9 (16,9%)	8 (17,4%)
Infarct location		
Anterior	23 (43,4%)	20 (43,4%)
Inferior	26 (49,0%)	23 (50,0%)
Other	4 (7,5%)	3 (6,5%)
Time from symptom onset to randomisation		
<2 h	13 (24,5%)	12 (26,1%)
>2 but <4 h	26 (49,0%)	23 (50,0%)
>4 but <6 h	14 (26,4%)	10 (21,7%)
Haemodynamics		
Median systolic blood pressure (mm Hg)	132,0 (120,0–150,0)	135,0 (120,0–150,0)
Median diastolic blood pressure (mm Hg)	80,0 (70,0–90,0)	80,0 (70,0–90,0)
Median heart rate (beats/min)	76,0 (65,0–88,0)	76,0 (65,0–88,0)
Number with heart failure		
Killip class I	28 (52,8%)	26 (56,5%)
Killip class II	16 (30,1%)	17 (36,9%)
Killip class III	7 (13,2%)	2 (4,3%)
Killip class IV	2 (3,7%)	1 (2,1%)

Tab.1 *Baseline characteristics.*

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Продолжительная антикоагуляционная терапия гепарином при инфаркте миокарда

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Р Е З Ю М Е

Поиск более эффективных и совершенных препаратов при лечении острого инфаркта миокарда является весьма актуальной задачей современной кардиологии. Цель исследования состояла в сравнении длительной и краткосрочной антикоагулации гепарином при остром инфаркте миокарда на фоне фибринолизиса стрептокиназой. Обследовано 99 пациентов с острым инфарктом миокарда - с ST элевацией, которым проводилась инфузия гепарина в течение 48 часов (n=53) и более длительно - 96 часов (n=46) вместе с тромболитической терапией (стрептокиназа, стандартная доза, которой составляла 1,5 миллиона). Первичной цель исследования – опредeлелить уровни смертности после 30 дней и внутригоспитального реинфаркта. На 30 день исследования, погибло 5 пациентов (9,4%) леченных гепарином в течение 48 часов и 4 пациента (8,7%) леченных гепарином в течение 96 часов. Установлено значительное снижение реинфаркта в течение госпитализации у пациентов, принимающих гепарин длительно в сравнении с больными, получавшими этот коагулянт кратковременно (t<0,05). Полученные данные свидельствуют, что длительное проведение антикоагуляции снижает смертность по сравнению с с краткосрочным применением гепарина и снижает частоту реинфаркта в течение госпитализации

Ключевые слова: *гепарин, антикоагуляция, фибринолизис, инфаркт миокарда*