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Accelerated streptokinase in ST-elevation myocardial infarction — a romanian (ASK–ROMANIA) multicenter registry

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Abstract

Background: The classical streptokinase regimen (1.5 M.U. over 60 min) may be too slow in patients with ST-elevation myocardial infarction (STEMI).
Objective: To compare the efficacy and safety of four streptokinase regimens in STEMI patients.
Methods: 1880 consecutive patients admitted within 6 h of STEMI onset were allocated one of the following four streptokinase regimens: 1.5 M.U. over 60 min ($n=517$); 1.5 M.U./30 min ($n=355$); 1.5 M.U./20 min ($n=507$); 0.75 M.U./10 min, repeated or not after 50 min if no electrocardiographic criteria of reperfusion ($n=501$).
Results: Rates of coronary reperfusion (non-invasively detected) for SK1.5/30 (72.39%), SK1.5/20 (75.34%) and SK0.75/10 (72.85%) were similar and higher than for SK1.5/60 (64.03%, $p=0.019$, $p<0.0001$, and $p=0.006$, respectively). In-hospital mortality was significantly lower for SK1.5/20 (7.10%) and SK0.75/10 (7.38%) and at the limit of significance for SK1.5/30 (7.60%) compared with SK1.5/60 (11.60%, $p<0.0001$, 0.006, and 0.053, respectively). Intracerebral haemorrhage and other major bleeding had similar incidence in the four groups.
Conclusions: Compared to the classical 1.5 M.U. over 60 min streptokinase regimen, significantly higher rates of coronary reperfusion and lower in-hospital mortality can be obtained by infusing the same dose over only 20 min, or either one or two half doses over only 10 min, without risk increase.

Keywords: Thrombolysis; Streptokinase; Acute myocardial infarction; Coronary reperfusion

1. Introduction

Thrombolytic therapy significantly decreases mortality, reduces the infarction area and results in better preservation of myocardial contractility in patients with ST-elevation myocardial infarction (STEMI) [1–8].

Efforts to improve the efficacy of the thrombolytic therapy in STEMI have resulted in the testing of faster regimens of alteplase (tPA) [5,9], of tPA derivatives — reteplase [10–13], lanoteplase [14,15] tenecteplase [16–18], of staphilokinase [19] and saruplase [20] in combination with unfractionated heparin [3–6,9–20], enoxaparin [21–23], hirulog [24] or abciximab [18,25]. A significant increase in the

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Thrombolysis in Myocardial Ischemia (TIMI) grade 3 rate of coronary reperfusion was reported with these combinations as compared with streptokinase [5,6] and alteplase [10,11,14–17]. However, none except one [5] of the studies comparing two or more thrombolytic regimens demonstrated the superiority of any regimen in reducing mortality [3,4,12–14,18,21–25]. GUSTO-1 study reported a 1% absolute reduction in 30-day mortality with an accelerated tPA regimen compared with streptokinase 1.5 M.U./60 min [5]. However, this study was controversial [26–28], as thrombolytic protocol had not always been adhered to [29].

The recommended streptokinase regimen consists in infusion of 1.5 M.U. over 30–60 min [30]. All major streptokinase trials used, however, only the slow infusion of this dose in 60 min [1–5,12,20,22,24,30]. Some data [31–34] and a personal experience accumulated before 1994 in the Spitalul de Urgență "Floreasca", Bucharest, suggested us that a faster infusion would increase the efficacy of streptokinase. The objective of this study was to test the hypothesis that a faster streptokinase infusion may result in a higher rate of coronary reperfusion and a lower mortality with no additional risk.

2. Methods

Between January 1st, 1994 and December 31st, 2005, a group of 3099 consecutive patients with STEMI (chest pain of at least 30 min duration and the ST-segment elevation $\geq$1 mm. in two or more contiguous limb leads and more than 2 mm. in two or more thoracic leads on the 12-lead ECG) received thrombolytic therapy in the six participating centers, as follows: center 1:1743 patients; center 2:441 patients (joined since 1.01.1998); centers 3 and 4 (369, respectively 330 patients, both since 1.01.1999); center 5:127 patients (since 1.01.2002) and center 6: 49 patients (since 1.01.2005).

In all centers, the choice of treatment schedule is currently left to physician preference, not restricted to the options outlined in this study.

Based on personal preference, treating physicians selected one of the following protocols: 1. Streptokinase 1.5 M.U. infused in 60 min; 2. Streptokinase 1.5 M.U./30 min; 3. Streptokinase 1.5 M.U./20 min; 4. Streptokinase 0.75 M.U./10 min followed or not after 50 min by a second infusion of 0.75 M.U./10 min if no ECG signs of coronary reperfusion were detected; 5. alteplase (15 mg in bolus followed by an infusion of 50 mg in 30 min and 35 mg over the next 60 min; 6. reteplase 10 i.u. in bolus followed after 30 min by another bolus of 10 i.u. All patients received aspirin on admission and during hospitalization, beta-blockers, ACE-inhibitors, statins, nitrates, and unfractionated heparin or enoxaparin in the absence of contraindications. Heparin (1000 i.u./h) was started immediately after thrombolytic administration, and was continued for 48–72 h with dose adjustments to maintain an activated partial thromboplastin time of 50 to 75 s.

For patients treated with enoxaparin, a 40 mg intravenous bolus was administered immediately before or after the thrombolytic infusion. Subsequently, 1 mg/kg bodyweight was administered subcutaneously at 12-h intervals for 5–8 days, the first dose at 12 h after the intravenous bolus.

In patients treated with streptokinase 0.75 M.U./10 min, the unfractionated heparin or the enoxaparin bolus was administered immediately after the first dose of 0.75 M.U.

All patients gave written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

We excluded patients who had undergone pacemaker implantation or coronary artery bypass graft or angioplasty in the past.

Coronary reperfusion was assessed clinically, electrocardiographically, and physiologically. The intensity of chest pain was evaluated every 10 min during the first 180 min from the start of thrombolysis using a subjective scale ranging from 0 (absence of pain) to 10 (unbearable pain). Clinical reperfusion was defined as sudden disappearance of pain in the first 180 min of thrombolysis.

All patients underwent continuous ECG monitoring using the lead indicating the highest ST-segment elevation. Concomitantly, standard 12-lead ECGs were recorded at the start of thrombolysis and at 10- to 15-min intervals over the following 180 min. Additional ECGs were recorded when sudden ST-segment modifications or reperfusion arrhythmias were detected, and at 24-h intervals throughout the hospital stay. Electrocardiographic reperfusion was defined as the reduction of the sum of ST-segment elevations by more than 50% of the initial value in the first 180 min of thrombolysis.

Plasma creatine kinase and creatine kinase MB isoensyme were measured at the start of thrombolysis and 4, 9, 12, 16, 20, 24, 36, 48, 72 and 96 h thereafter. Physiological coronary reperfusion was defined as a rapid elevation of creatine kinase MB isoensyme with a peak in the first 12 h after thrombolysis.

Patients were considered to have coronary reperfusion only if all three criteria were met. However, in patients in whom left bundle branch block precluded proper ST-segment analysis we used only the clinical and the physiological criteria.

Blood pressure was automatically measured at the beginning of streptokinase infusion and every 2 min thereafter for the next 20 min. The time interval for subsequent blood pressure recording was established by the physician. Streptokinase-induced hypotension was defined as systolic blood pressure decrease by more than 20% within 20 min of starting SK infusion. The speed of the streptokinase infusion was maintained in all patients who experienced this event. A saline solution was rapidly infused as soon as the streptokinase-induced hypotension was detected.

Major hemorrhage was defined as bleeding resulting in death, requirement for transfusion of at least two units of blood, a decrease in hemoglobin levels by 5 g/dL, or an intracranial, intraocular, or retroperitoneal hemorrhage. A computerised tomography was performed in all patients with