Angiographic patency study of an albumin-free recombinant streptokinase formulation in acute myocardial infarction.

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ABSTRACT PURPOSE. Fibrinolytic therapy restores coronary patency and reduces mortality in patients with acute myocardial infarction. Albumin is present in most of the streptokinase formulation as a stabilizer but it is not known whether it plays a role in the product's efficacy and safety profiles. The aim of this study was to assess 90 minutes-coronary patency of a new albumin-free recombinant streptokinase (rSK) formulation. **METHODS.** Patients with ischemic chest pain and ST-segment elevation, less than 12 hours after symptoms onset, without contraindications for fibrinolytic therapy, were included to receive 1.5 x 10^6 IU of rSK in a one-hour intravenous infusion. Angiography was performed 90 minutes after and coronary patency was classified according to the TIMI flow scales. **RESULTS.** The study enrolled 25 patients, 59.4 ± 9.2 years-old, 88% men and 92% white. The mean time interval between the symptoms onset and rSK infusion was 3.0 ± 2.0 hours. Patency rate (TIMI 2-3) of the infarct-related vessel was 72% (18/25). Partial or complete ST-segment resolution was achieved in 17 patients (68%). Hypotension and nauseas were the most frequent adverse events. Haemorrhage or in-hospital deaths were not reported. **CONCLUSIONS.** This study suggests that intravenous albumin-free rSK is a safe and appropriate therapy to get early (90-minute) coronary patency in patients with acute myocardial infarction.

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INTRODUCTION

Streptokinase (SK) is a commonly used fibrinolytic agent whose efficacy with regard to mortality reduction in patients with acute myocardial infarction (AMI) was demonstrated in large, placebo-controlled trials (1, 2). Long term follow up has provided clear evidence that the early survival advantage persists for at least 10 years after treatment (3, 4). Despite the fact that recombinant tissue plasminogen activator (rtPA) is preferred in some countries, SK is still the most worldwide used thrombolytic mainly due to its favourable cost-benefit ratio.

A streptokinase produced by means of recombinant DNA techniques (rSK) has been evaluated previously in clinical trials in AMI patients. The proof-of-concept study in term of angiography data showed a coronary recanalization (TIMI 2 and 3) in 14/20 (70%) patients after intracoronary administration (5). This result was further supported by the Thrombolysis with Recombinant Streptokinase in Acute Myocardial Infarct (TERIMA)-1 trial, a multicenter, randomized, comparative study of rSK vs. natural SK in 224 patients (6). Both SK were similar with respect to coronary patency at 8 days, changes in haemostasis, and anti-SK antibodies titre and their anti-SK neutralizing activity (7). The effect on in-hospital mortality of patients with AMI was evaluated in the TERIMA-2 study, a multicenter, phase IV clinical trial (8). In-hospital 10.4% mortality was found which represents a 4% absolute and a 28.3% relative lethality reduction as compared to a survey made before rSK treatment was introduced.

The further extension of this treatment in the country was monitored through an appropriate pharmacovigilance system, where a similar post-marketing safety

profile to those suggested in previous clinical trials was observed (manuscript in preparation).

Usually, SK formulations are stabilized with human serum albumin in an important proportion (10:1) with respect to SK protein content. However, this agent can pose additional safety concerns for the product. On one hand, being a hemoderivate and despite the quality assurance and control measures taken by the manufacturers, there is always a potential risk of viral contamination. In fact, some regulatory agencies are reluctant to accept albumin-containing products. On the other hand, albumin can form complexes with other macromolecules (9), which increase their immunogenicity (10). This has been found for streptokinase (11). Therefore, a stable albumin-free preparation has been recently developed. This pilot study was conducted to assess the coronary patency at 90 minutes as well as an overall safety profile of intravenous albumin-free rSK formulation in patients with AMI.

METHODS

The study was performed at the Institute for Cardiology and Cardiovascular Surgery (ICCS), a tertiary-care facility. Patients, any age and gender, were eligible if they had thoracic pain of suspected ischemic origin lasting between 30 minutes and 11:30 hours, not relieved by nitro-glycerine, and ST segment elevation (>1 mm in 2 limb leads and/or >2 mm in 2 precordial leads) in the electrocardiogram (ECG). Main exclusion criteria were those described in previous trials of rSK in AMI patients such as haemorrhage-risk situations, diastolic blood pressure $>$ 110 mm Hg, systolic blood pressure $<$ 95 mm Hg, and antecedent of streptokinase administration within the past 6 months. Patients with contraindications for coronary angiography on admission were not included either.

The study was approved by an independent Ethic Committee and by the Cuban Regulatory Authority. Written informed consent was asked for coronary angiograms but not for the thrombolysis, following the procedure adopted in the GISSI (1), and previous TERIMA trials (6, 8), since it was thought that the patients` or their relatives` psychological status would not allow them to be in adequate conditions to give an appropriate answer and also because the efficacy and safety profile of rSK compared to natural SK were similar in the previous trials (6, 12). The study complied with the Declaration of Helsinki.

All patients were treated with rSK (Heberkinasa, Heber Biotec, Havana) formulated in albumin-free preparation at 1 500 000 IU diluted in 100 mL saline, through a peripheral vein during 1 hour. Oral acetyl salicylic acid and beta-blockers were administered when there were no contraindications, while other drugs were left to the attending physicians' criteria.

At least the following ECG traces were obtained: baseline, 60 minutes after the start of infusion, after coronariography, 24 h, and then daily up to five days. Serum creatine kinase was measured during 3 days to confirm AMI diagnosis in patients with non Q-wave infarction. AMI was confirmed when new Q waves appeared in the ECG or when the enzymes increased above twice the upper reference value. Clinical evaluation was done daily while in-patients.

Primary endpoint was coronary patency at 90 minutes. The coronary angiograms were performed by members of the ICCS Cardiovascular Haemodynamic Group. The films were reviewed and the coronary patency was classified according to the TIMI flow scale (13). Percutaneous transluminal coronary angioplasty with stent implant was performed after the 90-minute angiogram in patients who had less than TIMI 3 perfusion. Secondary endpoints were ST-segment elevation regression at 90 minutes, complete chest pain resolution, death and reinfarction while in-hospital. The ST segment resolution was classified as complete ($\geq$ 70%), partial (30-70%) and no resolution ($<$ 30%) (14).

Adverse events were identified by patients` direct evaluation during and after SK administration. A qualitative assessment was used to classify the causal relationship as definite, probable, possible or doubtful (15). The severity of the adverse events was classified upon three levels: (a) mild, if no therapy was necessary, (b) moderate, if specific treatment was needed, and (c) severe, when hospitalization or its prolongation was required, and if the reaction was life-threatening or contributed to patient's death. Arterial hypotension was diagnosed when systolic pressure decreased below 90 mmHg or when a 20-mmHg reduction (as compared to basal values) was noted during the infusion or up to 2 h afterwards.

Data were double entered and validated on Microsoft Visual FoxPro version 5.0 and then imported into SPSS version 11.5 for further analysis. Continuous variables are expressed as mean ± standard deviation or median ± interquartile ranges. For this pilot study, 25 patients were chosen as the sample size in order to get the first estimation of thrombolytic efficacy and safety. This size permitted to estimate an expected 0.7 ± 0.2 patency rates (95% confidence interval).

RESULTS

Patient characteristics

Twenty five patients were included, of whom 22 (88%) were male and 23 (92%) were white. The baseline characteristics are shown in Table 1.

Table 1: Baseline characteristics of patients.

Characteristic	n (%) patients*
Gender male/female	22 (88)/3 (12)
Race white/no white	23 (92)/2 (8)
Mean age (years)	59.4 ± 9.2
Time symptom onset-infusion (hours)	3.0 ± 2.0
Infarction localization	
Inferior	15 (60)
Anterior	6 (24)
Anteroseptal	2 (8)
Inferolateral	2 (8)
Risk factors	
Hypertension	17 (68)
Smoking	13 (52)
Obesity	5 (20)
Alcoholism	5 (20)
Hyperlipidemia	5 (20)
Previous myocardial infarction	2 (8)
Diabetes mellitus	2 (8)

* Continuous variables are represented as mean ± standard deviation

The main causes of non inclusion were patients' admission after 12 hours of symptoms onset and haemorrhage-risk conditions. AMI was confirmed in all patients, 16 (64%) with Q-wave and the rest by enzymes only. Age ranged between 30 and 82 (59.4 ± 9.2) years. Mean time interval between symptoms onset and SK infusion start was 3.0 ± 2.0 hours. Inferior wall infarction was the commonest (60%). Diverse risk factors for coronary artery disease were identified, leaded by arterial hypertension. All patients were classified as Killip class I at inclusion.

Efficacy

All patients completed the coronary angiography study successfully without complications and had an assessable TIMI flow. The median time interval between thrombolysis and angiography was 90.0 minutes. In one patient, angiography was delayed up to 14 hours because of arterial hypotension. The infarct was related to the right coronary artery in 56% and to the left anterior descending artery in 36% (Table 2).

Table 2: Summary of outcomes.

Characteristic	n (%) patients
Time to coronariography in minutes*	90.0 ± 10.0
Affected artery	
Right coronary	14 (56)
Left anterior descending	9 (36)
Circumflex	2 (8)
TIMI flow grade	
Grade 0	6 (24)
Grade 1	1 (4)
Grade 2	4 (16)
Grade 3	14 (56)
ST segment resolution at 90 min	
No resolution	8 (32)
Partial resolution	8 (32)
Complete resolution	9 (36)
Chest pain resolution	17 (68)
Hospitalization time (days)†	8.2 ± 2.3

*median ± quartiles

† mean ± standard deviation

Patency rate (TIMI flow 2 + 3) of the infarct-related vessel was 72%. The 95% confidence interval for this estimate is 53 – 91%. Partial and complete ST-segment resolution in the electrocardiography at 90 minutes was observed in 8 (32%) and 9 (36%) patients, respectively. Complete chest pain resolution after SK treatment was achieved in 17 (68%) patients. All patients were alive at discharge. Other cardiovascular events as reinfarction, cardiogenic shock or heart failure, were not observed.

Safety

A total of 18 adverse events were described in 10 patients. Hypotension (20%) was the most frequent adverse event and its appropriated control included infusion rate reduction, Trendelenburg's position and volume expansion. Other adverse events, observed in more that one patient were nausea, vomiting, tremors, chills and bradycardia. Haemorrhage, which is one of the most significant complications of fibrinolytic therapy, was not found. Streptokinase was well tolerated and only one patient required discontinuation of infusion because of arterial hypotension. Although this patient received about half of the recommended dose (700 000 IU), angiography assessment at 14 hours after infusion showed TIMI 3 flow associated with complete ST and chest pain resolution (Table 3).

Table 3: Adverse events.

Adverse event	n	%
Hypotension	5	20
Nauseas	3	12
Vomiting	2	8
Tremors	2	8
Chills	2	8
Bradycardia	2	8
Headache	1	4
Ventricular fibrillations	1	4
No adverse event	15	60

Ten (55.5%) adverse events were classified as mild, whereas 7 (38.9%) were considered as moderate. One patient with ventricular fibrillation had the only severe adverse event. It was managed adequately after treatment with cardioversion and epinephrine. All suspected adverse events were assessed as being probably or possibly associated with the study medication.

DISCUSSION

This clinical trial was carried out to study the effect of an albumin-free formulation of rSK on coronary patency at 90 minutes in patients with AMI. The results of this initial experience, suggest that the albumin-free formulation of rSK is an efficacious therapy to generate early coronary permeability.

Coronary patency for an albumin-containing formulation of rSK was evaluated both after intracoronary and intravenous routes of administration. In the latter, a 67.1% of TIMI flow 2 and 3 was achieved in the coronary angiograms performed between 5 and 10 (median 8.0 ± 2.7) days after thrombolysis (6). However, this was a late evaluation and other factors apart from the pharmacological thrombolysis could have influenced on the patency rate. The present study is the first report of early patency after intravenous infusion with this product and the results (53 – 91% patency rate) are consistent with the literature. A recent pooled analysis of several trials reports a 48 – 55% patency rate 90 min. after SK intravenous infusion (16). Early restoration of coronary flow through the infarct-related artery results in improved ventricular performance and lower mortality among patients with AMI (17). Time between symptoms onset and treatment is a critical variable for success of thrombolysis (18), and could be a factor that influenced favourably the results obtained in this study.

The most common adverse event associated to rSK therapy was hypotension. The rate of this event is in accordance with those described in previous studies for the albumin containing formulation, where 20-24% of patients experienced this reaction (6, 8). Hypotension has been described as a transient event that may be related to the rate of SK infusion (19, 20), and it is recommended to reduce the infusion rate as initial manage. This event may also be explained by the pathophysiology of AMI or by other commonly used concomitant drugs, therefore it was difficult to establish a causal relationship with the study medication. Other important adverse events were arrhythmias, which have been considered as reperfusion sign during thrombolytic therapy (21), but are also a significant complication in the course of AMI. Haemorrhage, which is one of the most severe adverse reactions of fibrinolytic therapy, was not observed.

The new formulation will certainly solve the disadvantage related to the use of a blood derivative as a stabilizer. In this way, the product will only contain highly purified, known-composition components. Additionally, the formation of aggregates between rSK and albumin would also be avoided. These aggregates can enhance the immunogenicity of rSK, as has been described for other recombinant proteins such as interferon (9, 10). In fact, a significant raise of anti-SK antibodies and neutralization titres lasting for 6 months or more have been reported after infusion of albumin containing formulations of both recombinant and natural SK (7). These antibodies can cause allergic reactions or even neutralize a further SK dose with the subsequent decline in effectiveness. Interestingly, allergic reactions were not reported in this study versus approximately 2 – 6% with albumin-containing SK formulations (1, 2, 6, 8, 22), although a larger trial is needed to confirm this potentially better safety profile.

Even though it is recommended to use other thrombolytic agents such as rtPA in patients who present early after onset of chest pain or symptoms and in those with previous administration of streptokinase and at low risk of intracranial hemorrhage (23), this product is much more expensive than SK and not all countries can afford its general use, specially those with a general health reimbursement policy. That is why; SK is the first-line thrombolytic agent in many countries.

The favourable efficacy/safety profile achieved with rSK in this and previous studies, together with the adequate cost, justify the extent of this treatment in clinical practice as preference reperfusion therapy for AMI patients. A large controlled study is needed to confirm the results obtained with the new albumin-free formulation. Also, the national, spontaneous reporting-base pharmacovigilance program for streptokinase will give further information concerning the safety profile of this drug.

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