REFERENCES


INDIGENOUS RECOMBINANT STREPTOKINASE VS NATURAL STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION PATIENTS: PHASE III MULTICENTRIC RANDOMIZED DOUBLE BLIND TRIAL

S. K. DIWEDI, J. S. HIREMATH1, P. G. KERKAR2, KRISHNA N. REDDY3, C. N. MANJUNATH4, S. S. RAMESH5, S. PRABHAVATI4, M. DHOBE1, KAVITA SINGH6, P. BHUSARI6, RAMAN RAO6

ABSTRACT

BACKGROUND: Streptokinase is the most widely used thrombolytic agent and can now be made using recombinant DNA technology. The present trial was initiated to assess an indigenous recombinant streptokinase (Shankinase, r-SK). AIM: To compare the efficacy and safety of indigenous recombinant streptokinase (Shankinase, r-SK) and natural streptokinase (Streptase, n-SK). SETTINGS AND DESIGN: Double blind, randomized, non-inferiority, multicentric, parallel study. MATERIALS AND METHODS: Patients of AMI < 6 hours of chest pain and 2 mm ST elevation in 2 contiguous chest leads V1-V6 or 1 mm in limb leads were randomized to receive 1.5 miu of either r-SK or n-SK. CK Peaking and decrease of >50% ST segment were used to assess reperfusion. STATISTICAL ANALYSIS: Difference in the groups was assessed by chi-square or paired t test as required. Probability value <0.05 was considered significant with 95% confidence interval.

RESULTS: Overall 150 patients were recruited (96 r-SK group and 54 in n-SK group) and demographic and clinical profile of the groups was comparable. Reperfusion was seen in 68.2% (58) and 69.4% (34) patients in r-SK and n-SK groups respectively. Commonly seen adverse events were fever in 7 (8.5%), hypotension in 3 (3.6%), nausea in 2 (2.4%) patients. Minor bleeding were seen in 4 (4.8%) of patients. CONCLUSION: Indigenous recombinant Streptokinase (r-SK) is as efficacious as natural streptokinase (n-SK) in establishing reperfusion as assessed by non-invasive parameters with comparable side effect profile.

KEY WORDS: Streptokinase, Recombinant streptokinase, Myocardial infarction, Thrombolysis

INTRODUCTION

Over the last few years intravenous thrombolysis has become the standard therapeutic approach for patients with acute myocardial infarction (AMI). Intervention with thrombolytic agents in acute myocardial infarction is an effective means of limiting...
MATERIALS AND METHODS

Sigma Diagnostics Creatinine Kinase Kit (Procedure No. 47-UV, Sigma Diagnostics, US) after infusion. CK activity was estimated by regulatory requirements (schedule Y of drugs and cosmetics act 1940, where a study drug administration of Streptokinase and then again at 90 mins, 6 hrs, 12 hrs, 24 hrs and 36 hours.

Venous blood samples were collected before and also the side effects.

Statistical analysis

Determination of CK

Venous blood samples were collected before administration of Streptokinase and then again at 90 mins, 6 hrs, 12 hrs, 24 hrs and 36 hours after infusion. CK activity was estimated by Sigma Diagnostics Creatinine Kinase Kit (Procedure No. 47-UV, Sigma Diagnostics, US).

ECG assessment

Standard 12 lead ECG was done immediate before and 90 minutes after initiation of Streptokinase infusion and was assessed and interpreted by two different observers to avoid bias in reporting. Lead with maximum ST segment elevation was identified and level of ST segment elevation was measured immediately prior to and 90 min after initiation of therapeutic therapy.

Pain relief assessment

The percentage decrease in pain was recorded at 90 minutes after initiation thrombolytic therapy on a scale of 0-10 as perceived by the patient.

Other investigations

Serum samples were collected wherever possible for detecting anti-streptococcal antibodies. Pre discharge Echocardiogram was done to assess left ventricular function.

Liver function and renal function tests of all patients were carried before and after therapy. In case of bleeding episodes hemoglobin drop in hemoglobin of greater than 2 g/dl. 50% after 90 minutes of thrombolysis was also considered an indicator of reperfusion.

Pre discharge Echocardiogram was done to assess left ventricular function.

Statistical analysis

The sample size was determined as per regulatory requirements (schedule Y of drugs and cosmetics act 1940, where a study drug
has to be evaluated in at least 100 subjects). The difference in both the groups was assessed by the chi-square and paired t test wherever required. A probability value <0.05 was considered to be significant with 95% confidence interval. The SAS version 8.2 (SAS Institute Inc, Cary, NC, US) software was used to carry out the statistical analysis.

RESULTS
Clinical data
Between January 2003 to June 2003, 150 were patients recruited in the study while 96 received recombinant 54 patients were administered natural streptokinase. As per protocol 85 out of 96 and 49 out of 54 patients were eligible for evaluation for efficacy while as per intention to treat all 150 were evaluated for safety. The organizational chart of the recruitment of the patients is represented in Figure 1. There was no significant difference in the demographic and clinical profile of patients in both the groups [Table 1]. Mean symptom-treatment interval was 3.6±2.5 hrs and 3.8±2.1 hrs for Shankinase and Streptase respectively.

Reperfusion
CK peaking less than or at 12 hours was seen in 83.5% (71) and 89.8% (44) patients in r-SK and n-SK group respectively. The kinetics of CK peaking at different intervals in both the groups is represented in Figure 2. ST segment resolution ≥50% was observed in 81.2% (69) and 79.6% (39) patients in r-SK and n-SK group respectively. Pain resolution in 94.1% (80) and 93.9% (46) of patients in r-SK and n-SK group respectively. Reperfusion as assessed by the combination of CK peaking and ST resolution ≥50 was seen in 68.2% (58) and 69.4% (34) in r-SK and n-SK groups respectively. When assessed by all three parameters reperfusion rates where 69.0% (59) and 65.3% (32) in r-SK and n-SK respectively (P=0.652) [Table 2].

Overall 47 serum samples were tested (27 from r-SK and 20 from n-SK group) for Anti-streptococcal antibodies. As is evident from the Table 3 presence of anti-streptococcal

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<th>Table 1: Demographic and clinical characteristics of patients</th>
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<td>Recombinant Streptokinase (%)</td>
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<td>Age (year, mean ± SD)</td>
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<th>Table 2: Efficacy parameters seen in both groups</th>
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<td>CK Peakings ≤12 hours</td>
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<td>ST resolution ≥50%</td>
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<td>Pain resolution</td>
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<td>CK and ST resolution</td>
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<td>CK, ST resolution and pain relief</td>
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antibodies did not interfere with the reperfusion, in either of the groups.

The occurrence of reperfusion arrhythmias was observed in 25% of patients in both the groups. The most commonly seen arrhythmias were accelerated idoventricular rhythm (AIVR) (38.8%), ventricular premature beats (38.8%) and ventricular tachycardia (22.2%).

Adverse Events
No significant differences were observed in the adverse event profile between the two groups although hypotension and fever were relatively common (Table 4). Hypotension in all the patients responded to introtopes and saline infusion after transient cessation of therapy.

Fever of moderate grade and was accompanied by rigors in three patients in r-SK group. All patients were given antipyretics and responded to therapy. Nausea and vomiting which was seen in 2 and 3 cases respectively in the two groups was controlled by administration of antiemetics.

Overall eight bleeding episodes were reported of which only one was major bleeding in the n-SK group, the remaining 7 were minor events 4 and 3 events in the r-SK and n-SK groups respectively. One patient who had a major gastrointestinal bleeding needed blood transfusion he also had Thrombocytopenia, which subsided on stoppage of heparin. Of these four events in the r-SK group two patients had bleeding at the site of venipuncture, which later healed without any need for medication, one patient had gastrointestinal bleeding, who was managed conservatively, while another patient had an episode of gum bleed followed by haemoptysis, which did not recur. Of the three events reported from the n-SK group two were cases of minor oozing at the site of venipuncture, which resolved without medication, one patient had gastrointestinal bleeding without hemodynamic compromise and was managed conservatively.

DISCUSSION
Reperfusion in the present study which was the primary end point was assessed using a combination of enzyme (Creatine Kinase) peaking and ST segment resolution was observed in 68.2% (58) in the r-SK and in 69.4% (34) patients in n-SK group whereas, rates reported in literature by the present criteria vary from 59 to 82%. A randomized comparative study was carried out in over 200 patients where a reperfusion rate of 67.1 and 70.7 was observed with recombinant and natural streptokinase respectively.[14-6,15] A similar rate of 70.6% was reported from previous Indian studies with natural streptokinase.[16] Safety profile assessment which was the secondary end point in the present study was similar in both the r-SK and n-SK group. These events seen were similar to those reported by other studies. Incidence of bleeding was 4.2% (4) in the r-SK group while it was 5.4% (3) in the n-SK group, which are similar to the rates reported in literature vary between 0.5 to 15.2%.[1, 5, 11-15] No anaphylactic reactions were seen in the r-SK group whereas one was reported from the n-SK group. Adverse effects of thrombolytic therapy commonly include hypotension 4.5-15%, fever 5%, rigors, nausea and vomiting 46% and bleeding (0.5-15.2%). The mortality rates were low for both the groups (3.1% (3) and 5.5% (3)), however the present small study did not have the statistical power to show the difference in the two comparable treatment groups. Post thrombolysis, cardiogenic shock was observed in 1 (1.2%) and 2 (3.6%) in the recombinant and natural streptokinase groups respectively whereas reinfarction was seen in 2 (2.4%) and 3.6%) patients respectively in both the groups which is much less than in other studies.

The present study has its limitations as the sample size is small and the markers used for assessing reperfusion were non-invasive instead of the gold standard that is angiography, although the non-invasive methods have been validated against angiography and are proven surrogate markers of reperfusion. Since this trial was a randomised controlled trial the instigators were of the opinion that the conditions to see the efficacy and safety need some factors to be controlled including patients not more than 65yers of age and without any co-orbid conditions that might influence the outcome. A larger study with patecny assessed by angiography and without influencing factors of age or others would give a precise assessment of reperfusion.

Streptokinase is the most widely used thrombolytic agent particularly in India while others like tPA are expensive. Reviews comparing other thrombolytic agents have shown that streptokinase to be as good as that of tPA or rPA in terms of both efficacy and safety.[14,15] Recombinant streptokinase has the advantage of not containing streptolysin and streptodornase unlike streptococci-derived natural streptokinase which might make it safer, and will be cheap which is very relevant to our country's population. This technology can be further used to make more modifications in the present agents to make them more safe and efficacious.
REFERENCES


ABSTRACT

Ascariasis is a common intestinal parasitic disease in many developing countries and is a common cause of biliary and pancreatic diseases in endemic areas. Numerous studies have been published on biliary tract ascariasis. All these have documented ultrasonography as the primary imaging modality for biliary tract ascariasis. Magnetic Resonance Cholangiopancreatography (MRCP) has been the latest entrant for the study of biliary tract ascariasis. MRCP findings of biliary tract ascariasis have been scarcely documented. MRCP is a unique non-invasive investigation for demonstrating ascariasis in Gall bladder and biliary tract clearly. We present MR appearances of Gall bladder and biliary tract in a proven case of biliary ascariasis.

KEY WORDS: Gall Bladder, Biliary Tract, Ascariasis, MRCP

INTRODUCTION

Ascariasis is a common intestinal parasitic disease in many developing countries and is a common cause of biliary and pancreatic diseases in endemic areas. From duodenum it can enter biliary tract where it is associated with biliary colic and ascending cholangitis. Cholecystitis, pancreatitis, obstructive jaundice and septicemia are the other potential complications. Ultrasound is the investigation of choice for detection of biliary ascariasis. MRCP is being increasingly used for evaluation of Pancreato-biliary system. There are very few reports documenting MRCP findings in biliary ascariasis. The MRCP findings in a proven case of biliary ascariasis are presented here. The role of MRCP in such cases is also briefly discussed vis a vis other imaging modalities.

CASE REPORT

A 16 years old girl presented with obstructive jaundice, fever and pain. Ultrasound revealed gallstones and dilated common bile duct (CBD) with suggestion of biliary ascariasis. MRCP was done for further revaluation.

The patient was subjected to MR examination...