ADVERSE EFFECT PROFILE OF STREPTOKINASE THERAPY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: A PROSPECTIVE STUDY.

Javid A Malik, G.Q. Khan

ABSTRACT

Active surveillance of adverse reactions to already marketed drugs must continue for the whole life span of the drug. Streptokinase (SK) is an extensively used thrombolytic agent for the management of patients with acute myocardial infarction (AMI). We conducted a prospective evaluation of the adverse effect profile of SK.

All patients admitted to the Cardiology Unit of Govt. Medical College hospital Srinagar, India with a diagnosis of AMI were eligible to participate in the study if they did not have any of the exclusion criteria. Eligible patients received 1.5 million units of streptokinase intravenously in normal saline over 1 hour. Blood samples were drawn for various hematological and biochemical investigations. Patients were meticulously monitored for all possible adverse effects, if any.

Out of 163 patients of AMI, 102 (62.5%) were thrombolysed. The two most common contraindications for thrombolysis were sustained B.P > 180/110 and presentation later than 12 hours. Thrombolysis was successful in 47% patients. Bleeding from various sites occurred in 11(10.7%) patients including 4 cases of upper gastrointestinal bleed and 2 cases of macroscopic haematuria. Hypotension and minor allergic reactions each occurred in 6 (5.8%) patients. We observed few unusual complications of streptokinase therapy like thrombocytopenia in 3 patients, subnephrotic proteinuria in 2, and non-oliguric acute renal failure(ARF) in one patient. Both thrombocytopenia and ARF were self-limited.

Conclusion: Streptokinase is a relatively safe drug with modest efficacy and has low incidence of life threatening adverse effects. Therefore its use should be encouraged whenever indicated in acute myocardial infarction, especially when primary PTCA is not available.

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INTRODUCTION

Streptokinase (SK) is an enzyme derived from certain strains of β-lactamolytic streptococci. It consists of a single polypeptide chain with a molecular weight of 47,000 daltons and contains 414 amino acids. Isolated in 1953, it was the first thrombolytic drug to be used and is the most widely prescribed and least expensive of the drugs used. It is usually administered intravenously to treat a wide range of diseases associated with pathological activation of haemostasis like acute myocardial infarction (AMI), pulmonary thromboembolism, deep vein thrombosis (DVT) and acute arterial occlusion. It is however in AMI that its use has been most widely studied with several large multicentric trials showing efficacy of thrombolytic therapy in general and of streptokinase in particular.

Being a foreign protein, SK is antigenic and is responsible for a variety of allergic reactions, including rash, hypotension, and serious anaphylactic reactions (urticaria, bronchospasm, angioedema). The most common complication of SK therapy is bleeding and the most catastrophic complication is intracranial haemorrhage (ICH) which has an incidence of approximately 0.1-0.5%.

Despite the easy availability and extensive use of SK in India, to the best of our knowledge, a prospective evaluation of its adverse effect profile in patients with AMI has not been done.

Key words: Streptokinase, Adverse effects, Thrombolysis, Acute myocardial infarction
Therefore, the present study was conducted with the main aim of evaluating the adverse effects associated with SK therapy.

The study was conducted in the Cardiology Unit of the Government Medical College Hospital, Srinagar, India. This is a 500-bed tertiary care hospital catering mainly the population of the state of Jammu & Kashmir. All patients admitted into the Cardiology Unit with a diagnosis of AMI were eligible to participate in this prospective study if they received thrombolysis with SK in the hospital.

AMI was diagnosed if two or more of the following were present: sudden development of prolonged (>30 minutes) anterior chest discomfort, electrocardiographically detected ST-segment elevation in two contiguous leads of at least 2mm, elevation of cardiac enzymes (CK-MB, troponin T) and appearance of segmental wall motion abnormality on echocardiography.

The study was conducted between March, 2001 and April 2002. During this period 163 patients of AMI were admitted, out of whom 102 (62.5%) were thrombolysed using 1.5 million units of SK in normal saline over one hour. Sixty one patients were excluded from the study; the reasons for exclusion are given in Table 1.

Disappearance of chest pain and resolution of ST segment elevation by two-thirds at 90 minutes post-thrombolysis with or without reperfusion arrhythmias were considered as indicators of successful thrombolysis. Patients who had reperfusion failure were referred for rescue percutaneous coronary intervention (PCI) to appropriate centers.

All those patients who received SK also received low molecular weight heparin (LMWH) for the next five days in addition to aspirin, angiotensin converting enzyme (ACE) inhibitors, α-blockers and statins. Blood samples were drawn for complete blood count (CBC), blood sugar, serum creatinine, CPK, AST, LDH, and lipid profile. Urine analysis and 24 hour urinary protein were ordered in all patients as was Troponin T. Patients were monitored for mechanical, electrical and fibrinolytic complications and further investigations and management was accordingly planned. Previous medical records wherever available were thoroughly reviewed. Upper GI endoscopy was done 1 month after discharge in 4 patients who developed gastrointestinal bleeds.

RESULTS

Baseline characteristics of all patients are given in Table 2. Out of the 102 patients of AMI who received SK, 29 (28.4%) developed complications related to this drug (Table 3). Overall the adverse effects were more common in males as compared to females (62% vs 38%).

The commonest complication observed was bleeding from various sites that occurred in 11 (10.7%) patients (Table 3). Bleeding from vascular puncture sites and gastrointestinal tract each of which occurred in 4 (3.9%) patients were the two most common sites followed by macroscopic haematuria 2 (1.9%) and a big haematoma into the medial aspect of the right thigh of a 70 year old diabetic female (Table 4). None of our patients developed ICH and there was no death directly related to SK thrombolysis. All the 4 patients who developed upper GI bleed were males, had a mean drop in haemoglobin of 4 g/dL and all of them needed blood transfusion. Upper GI endoscopy done one month after discharge from hospital was normal in all these 4 patients.

### Table 1

**REASONS FOR EXCLUSION OF PATIENTS FROM THE STUDY.**

1. Sustained BP > 160/110 at presentation
2. Past history of intracranial haemorrhage at anytime or non-haemorrhagic stroke within one year
3. Known intracranial neoplasm
4. Active internal bleeding (excluding menses)
5. Patient on oral anticoagulants with an INR > 2.5 and patients with known bleeding diathesis.
6. Active peptic ulcer and gastrointestinal bleeding in preceding 1 month
7. Suspected aortic dissection
8. Recent major surgery (< 3 wks)
9. Pregnancy
10. Streptokinase related thrombolysis (5 days to 2 years) or significant hypersensitivity reaction
11. Acute pancytopenia
12. Late presentation (i.e. more than 12 hours from the onset of symptoms)

### Table 2

**Baseline characteristics of the study patients (n=102)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No</td>
<td>58(57)</td>
<td>44(43)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>46(15)</td>
<td>51(13)</td>
</tr>
<tr>
<td>Range</td>
<td>32-78</td>
<td>44-76</td>
</tr>
<tr>
<td>Risk factor No (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>41(40)</td>
<td>37(36)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20(19)</td>
<td>18(17)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15(14)</td>
<td>20(19)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>14(13)</td>
<td>11(10)</td>
</tr>
<tr>
<td>Smoking</td>
<td>45(44)</td>
<td>11(10)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>30(29)</td>
<td>34(33)</td>
</tr>
<tr>
<td>No of drugs receiving at admission, mean (SD)</td>
<td>3(2.14)</td>
<td>3(1.6)</td>
</tr>
</tbody>
</table>

### Table 3

**ADVERSE EFFECTS OBSERVED IN STREPTOKINASE RECIPIENTS:**

<table>
<thead>
<tr>
<th>Complications</th>
<th>No (%)* of patients Mean Age</th>
<th>Male, No.</th>
<th>Female No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding from various sites</td>
<td>11(10.7%)</td>
<td>53</td>
<td>8(73)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6(5.8%)</td>
<td>52</td>
<td>3(50)</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>6(5.8%)</td>
<td>54</td>
<td>4(67)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3(2.9%)</td>
<td>46</td>
<td>2(67)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2(1.9%)</td>
<td>62</td>
<td>0(0)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1(0.9%)</td>
<td>47</td>
<td>1(11)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Zero</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deaths directly related to SK</td>
<td>Zero</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>29 (28.4%)</td>
<td>52</td>
<td>18 (62.2%)</td>
</tr>
</tbody>
</table>

*% denotes percent of all patients
**% denotes percent of patients with that particular adverse effect.
The second most common complication was hypotension that affected six (5.8%) patients including 3 males and 3 females who had a mean age of 52 years. It responded to reduction in the rate of SK infusion and 200 mg of intravenous hydrocortisone. Thrombocytopenia occurred in 3 (2.9%) of SK recipients—all were relatively young (mean age 46 years) and their mean platelet count was 60,000. Other cell lines were unaffected and platelet count normalized within 2 weeks.

Renal involvement in the form of subnephrotic proteinuria occurred in two female patients and non-oliguric acute renal failure (ARF) occurred in one patient. All the 3 patients had recently documented normal kidney function tests before they developed acute coronary syndrome. They were all non-diabetic, had no history of nephrotoxic drug intake and their collagen vascular disease profile was negative. A 47-year-old male who received SK within two hours of onset of chest pain and who’s BP remained normal throughout the hospital course developed non-oliguric ARF on the second day of AMI. He did not need any dialysis and regained normal kidney function tests within 10 days of hospitalization. However, the other two patients continued to have non-progressive subnephrotic proteinuria till the last out-patient follow up (3 months). Renal biopsy was planned if proteinuria persisted beyond six months. Thrombolysis was considered successful in 48 (47%) patients based on subsidence of chest pain and resolution of ST segment elevation by at least two-thirds at 90 minutes post-thrombolysis.

DISCUSSION

A collaborative overview of placebo-controlled trials of intravenous thrombolytic therapy, encompassing more than 60,000 patients has clearly shown that thrombolytic therapy is effective in all patients with AMI admitted to hospital within 12 hours of onset of symptoms.

The present study involved 102 patients of AMI who received SK (15 million units) within 12 hours of onset of chest pain. Successful reperfusion was achieved in 47% patients who received this drug. A quantitative scale known as Thrombolysis in Myocardial Infarction (TIMI) grading system that assesses the flow in the culprit artery (grade 3 flow being the goal of thrombolytic therapy) could not be applied since coronary angiography was not possible in our hospital. Coronary recanalization rates of 40-45% with SK and 65-70% with r-PA, (a more costly drug), are known. We observed SK related complications in 28.4% but no deaths directly related to it. The commonest complication (10.7%) that we encountered was bleeding from various sites including vascular puncture sites, gastrointestinal mucosa, haematuria and skeletal muscle. Bleeding is known to be the most common complication of SK therapy. Minor bleeding (not requiring transfusion) occurs in 3 to 4% of patients in the absence of invasive procedures.

Various series have reported that 70% of bleeding episodes occur at the sites of vascular punctures and microscopic hematuria and blood streaked sputum or vomitus are also noted. Significant or major bleeding (requiring transfusion) occurs in approximately 1% of patients. Intracranial haemorrhage (ICH), the frequency of which varies with the clinical characteristics of the patients and the thrombolytic agent used, is the most dangerous complication of thrombolytic therapy occurring at an incidence of 0.1 to 0.5%. In the present study, no such complication was observed.

### Table 4

<table>
<thead>
<tr>
<th>Site of bleeding</th>
<th>No. (%) of patients</th>
<th>Age (mean)</th>
<th>Sex (M:F)</th>
<th>Mean Hb drop GdL</th>
<th>Transfusion required, if any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular punctures</td>
<td>4(3.9%)</td>
<td>50</td>
<td>2.2</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Upper GI tract</td>
<td>4(3.9%)</td>
<td>65</td>
<td>4.0</td>
<td>4</td>
<td>2-4 units</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>2(1.9%)</td>
<td>50</td>
<td>2.0</td>
<td>4</td>
<td>2-4 units</td>
</tr>
<tr>
<td>Muscles and skin</td>
<td>1(0.9%)</td>
<td>70</td>
<td>0.1</td>
<td>4</td>
<td>2-4 units</td>
</tr>
<tr>
<td>Intracranial</td>
<td>Zero</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*% denotes percent of all patients

Transient hypertension is caused by SK in many patients, but significant allergic phenomena like bronchospasm, rash and serum sickness-like illness occur in only minority of its recipients. In our series 5.8% patients developed hypertension that responded to slowed rate of SK infusion and a bolus dose of short acting steroid.

Three relatively young patients developed thrombocytopenia with a mean platelet count of 60,000 that resolved within 2 weeks without any treatment. Thrombocytopenia may not be associated with SK therapy since all patients received low-molecular-weight heparin (LMWH) which is also known to cause thrombocytopenia although to a much lesser extent than the standard unfractionated heparin.

We also observed renal involvement in the form of subnephrotic proteinuria in two patients and non-oliguric ARF in a 47-year-old male patient. Proteinuria is common after SK treatment but it can uncommonly produce immune mediated glomerular injury leading to ARF, that is steroid responsive. Our patient had spontaneous recovery of renal function and did not need any steroid or dialysis, therapy.

In AMI patients receiving thrombolysis, particularly elderly treated later than 12 hours, there has been excess of deaths in first 24 hours compared to controls, a phenomenon called "early hazard". The exact mechanism of this early hazard is not clear, however various explanations include fatal ICH, myocardial rupture, reperfusion injury and inadequate reperfusion resulting in pump failure and cardiogenic shock.

Various studies have reported equal incidence of side effects with intracoronary SK and intravenous ansylolated plasminogen streptokinase activator complex (APSAC) in AMI patients, with bleeding as the most frequently encountered adverse effect particularly from femoral puncture site for angiography.

Unusual complications of thrombolytic therapy include aortic dissection, splenic rupture and cholesterol...
embolization To reduce the incidence of side effects of SK certain modifications of the drug like, light B chain SK, activator-complex and acylated activator therapy have been proposed. None of these preparations are available in India at present.

The study has several limitations, firstly, there was no control group that makes any attempt to qualitatively or quantitatively assess adverse effects difficult. However, since the efficacy of SK has been established, a placebo group could not be included. Secondly, it would have been appropriate to compare SK with alteplase as regards efficacy, safety and cost. This could serve as a useful guide for practitioners of developing nations regarding the cost-effectiveness of the two agents since there is a 12-fold difference in their retail price (approximately US $50 per 1.5 million units of SK versus US $600 per 50 mg of rtPA). However, no company would be willing to sponsor such a trial, and there will be few patients who can actually afford alteplase in order to carry out an open study.

BIBLIOGRAPHY

5. Fibrinolytic therapy trials (FTT) collaborative group. Indications for fibrinolytic therapy in suspected acute myocardial infarction. Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311-322
21. Rothbard RL. Comparative tolerance and complications in a multicenter trial of intracoronary streptokinase and intravenous anisoylated plasminogen streptokinase activator complex in acute myocardial infarction. Drugs 1987;33(suppl 3):276-8