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Research Article

STREPTOKINASE THERAPY IN PATIENTS PRESENTING BETWEEN 6-24 HOURS AFTER ACUTE MYOCARDIAL INFARCTION AND CAUSE OF LATE THROMBOLYSIS

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ABSTRACT
This study was conducted to study the in hospital morbidity and mortality in patients receiving thrombolytic therapy late (6-24hours) after acute myocardial infarction and to look into the factors responsible for the delay in starting the thrombolytic (reperfusion) therapy. In the study it was found that patients benefited from thrombolytic therapy including those patients who presented later than 6 hours with ongoing signs and symptoms of myocardial ischemia. Various reasons were identified for the delay in starting the thrombolytic therapy and every effort should be made to shorten the delay time period so that myocardium can be salvaged with early thrombolysis.

Keywords: *Streptokinase, Thrombolytic Therapy, Acute Myocardial Infarction, Late Thrombolysis, Late Presentation, Reasons Delay*

INTRODUCTION
Streptokinase (STK) is the first thrombolytic agent to be used in acute myocardial infarction (AMI). It is currently being administered to many thousands of patients with same condition (Jerry *et al.*, 1997). The greatest benefits occur when STK is given early, after the onset of symptoms although late benefits have been observed in patients treated after6 hours of onset of pain (Jerry *et al.*, 1997). Mortality was significantly lower among those patients with ST elevation given STK infusion 7-24 hours after onset of symptoms than those given a placebo (Colins *et al.*, 1988).
In many studies it has been seen that patients with acute myocardial infarction presented late after the onset of chest pain to the hospital. For various reasons, there are delays in starting the thrombolytic therapy with streptokinase in such patients. Thus, this study was aimed to look into the outcome of STK therapy in patients with AMI, presenting between 6 hours and 24 hours after the onset of symptoms and to look into reasons for late start of thrombolytic therapy.

Aims of the Study*:*
1. To study the in hospital morbidity and mortality in patients receiving thrombolytic therapy late (6-24hours) after acute myocardial infarction.
2. To look into the factors responsible for the delay in presenting to the hospital after the onset of symptoms of acute myocardial infarction.

MATERIALS AND METHODS
This was a prospective study of one year conducted in Christian Medical College and Hospital, Ludhiana, Punjab. All patients with AMI receiving streptokinase as a part of thrombolytic therapy between 6-24hours after the onset of presenting symptoms constituted the study group. Results were compared with those of patients receiving thrombolytic therapy for AMI who presented up to 6 hours after the presenting symptoms of AMI.
1. Diagnosis of AMI – was made on the basis of the following historical, clinical, EKG, and biochemical criteria. Patients were diagnosed to have AMI if they had any two of the three criteria.

A. History suggestive of AMI – namely, dull constricting or oppressive precordial pain over half an hour.
B. EKG changes-Deep pathological Q waves, either ST elevation or ST depression with or without T wave abnormalities in the form of deep and symmetrical T wave in any of the corresponding EKG leads on serial tracing.
C. Elevated cardiac enzymes-Troponin-T/CPK/AST/LDH characteristics of AMI without other clinical reasons for enzymes elevation.

Treatment Protocol

A. *Study Group:* Candidates for thrombolytic therapy presented between 4-24 hours of onset of pain with evidence of ongoing ischemia in the form of-
1) Persisting, recurrent intermittent chest pain [stuttering infarction]
2) Persisting ST elevation.
These patients constituted the study group.
B. *Control Group:* Results were compared with the outcome of patients who receive thrombolytic therapy for AMI within 6 hours if onset of symptoms. These patients constituted the control group.
C. *Thrombolytic Therapy*: Study group patients were given Inj. Streptokinase (STK) 15 Lac units intra venous (iv) as an infusion over a period of 1 hour. Injection Heparin was given as IV infusion 4Hours after STk infusion. Oral Aspirin, Clopidogrel, Statins and IV Nitroglycerine was given to all the patients within the first 48 hours, after that oral nitrates were given. Beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and iv magnesium was given as and when indicated.
2. Reasons for delay start of reperfusion therapy: a detailed evaluation was done to find out the reasons of delay in start of reperfusion therapy.

Contraindications to STK Therapy

All the patients who had one of the following conditions were not subjected thrombolytic therapy.
1. Age above 70 years
2. Presence of active bleeding
3. History of recent stroke (within 40 days), intracranial or intraspinal surgery.
4. Known intracranial neoplasm's or symptoms compatible with space occupying lesions.
5. Recent (within 15 days) surgery or gastrointestinal bleeding.
6. Recent trauma including mechanical cardiopulmonary resuscitation.
7. Known history of bleeding disorders, known hepatic diseases or renal diseases.
8. Prior severe allergic reactions to STK.
9. Shock with systolic blood pressure<80 mmHg.
10. Severe uncontrolled hypertension>200 mmHg. systolic or > 110 mmHg. diastolic, not controlled within 4-24hours time window.

Exclusion Criteria

a) Patients presenting before 6 hours and after 24 hours of onset of AMI (for the study group).
b) Concomitant congenital heart disease.
c) Concomitant Acute Pericarditis
d) Concomitant rheumatic valvular heart disease.

In Hospital Morbidity and Mortality

The following were studied for in hospital morbidity.
a) *CLINICAL*:
1. Post infarction angina.
2. Re-infarction
3. Clinical heart failure
4. Need for emergency interventional procedures Percutaneous Trans Coronary Angiography (PTCA) or bypass surgery.
5. Cardiac arrhythmia's-tachy/brady arrhythmia's
6. Thromboembolism

7. Pericarditis
8. Mechanical complications of AMI – VSD, MR
9. Bleeding complications – major/minor.
10. Renal failure.

b) *ECHOCARDIOGRAPHY*:-

i. LV size
ii. LV systolic function
iii. Regional wall motion abnormality
iv. LV clot
v. Pericardial effusion

In Hospital Mortality

Statistical Methods*:* Student – t test and chi square test was used for the analysis of the data as applicable.

Research Articles

Streptokinase (STK) is the first thrombolytic agent to be used in acute myocardial infarction (AMI). It is currently being administered to many thousands of patients with same condition. The greatest benefits occur when STK is given early, after the onset of symptoms although late benefits have been observed in patients treated after 6 hours of onset of pain (Jerry *et al.,* 1997). Sherry and Marder (1991) reviewed a number of studies using STK and tissue plasminogen activator (rt-PA) and concluded that a stable state of vessel patency is meaning for mortality reduction even after completion of the infarction. Such late but lasting patency is a critical component of the open vessel principle and explains, in part, the survival benefits that occur to patients treated with STK even after the onset of symptoms.

In the second international study of infarct survival (ISIS – 2, 1988), it was found that mortality was significantly lower among those patients with ST elevation given STK infusion 7-24 hours after onset of symptoms than those given a placebo (Colins *et al.,* 1988).

To help determine more reliably the 'time window' for worthwhile benefit from fibrinolytic therapy EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del sur) group-studied 4534 patients entering the hospital upto 24 hours after the onset of AMI; there was a trend towards fewer cardiac deaths among patients presenting even after 6 hours of onset of AMI (EMERAS study group, 1993).

Other beneficial effects of late reperfusion include a reduction in formation of left ventricular aneurysms (Hochman and Chooh, 1987). A reduction in ventricular instability and potentially lethal ventricular arrhythmia's was also noticed Kersschot *et al.,* (1986), Sagar *et al.,* (1988). The results supported the notion that late thrombolytic therapy may reduce the incidence of residual ischemia during the post infarction period (Grip *et al.,* 1991).

Late Assessment of Thrombolytic Efficacy (Late study group, 1993) concluded since 30% of patients with AMI arrive in hospital later than the commonly applied time limit for thrombolysis of six hours so an extension of this time window would make such therapy available to more patients and therefore recommends that all patients with AMI be treated up to 6 hours. These findings conjunction with ISIS – 2 provide encouraging evidence, that for some patients the benefits may extend up to 24 hours. A number of workers feel that thrombolytic therapy is being under-utilized in the management of AMI (David and Eric, 1990).

Bosarge *et al.,* (1995) in a coronary angiographic study of 50 patients found that STK given within 12 hours of chest pain is effective in achieving vessel patency and preservation of left ventricular function in patients if AMI.

Observations

This was a prospective study of 1 year. All patients receiving thrombolytic therapy between 6-24 hours after the onset of presenting symptoms constituted the study group (Group 1) and the results were compared with patients receiving streptokinase therapy within 6 hours of their presentation (Group 2). Various reasons for the delayed presentation to the hospital after the onset of AMI were also studied. In

this study a total of 176 patients were studied. 86 patients were enrolled in Group1 and Group2 respectively. Various clinical and lab tests were performed on these patients along with ECG and Electrocardiography.

1) Age of the patients ranged from 32 – 35 years, mean age was 56.66 +/- 9.71 years (p=>0.05)
2) 23 patients were below 50 years of age and 63 patients were above 50 years of age in group 1 (p=NS)
3) 63(73.3%) were males and 23% (26.7%) were females. The difference in the sex groups was not statistically significant (p=>0.05)
4) Time of presentation and No of patients:

i) Maximum no of patients came between 6am and 3pm, 96(55.81%)
ii) There were three (20%) deaths among total of 18 patients who presented between 9PM and 12PM in Group1 where as in group2 all the patients who presented within the same time duration here was no mortality.
iii) There was only one death in the time interval from 12PM to 3PM in both the study groups. In group2 all of the 19 patients who presented from 12pm to 3pm were discharged.
iv) In the time interval of 3PM to 6PM there was one mortality observed in group2 and none in group 1.
v) In the same interval 6PM to 9PM there was one mortality observed in group1 , where as there was no mortality in group2.
vi) In the time interval of 9PM to 12AM there was no mortality observed in either of the groups (p<0.05)

5 There were 54 patients who received streptokinase within 6-12 hours of onset of AMI, out of which 3 (3.48%) patients expired. There were 17 patients who received streptokinase within 12 to 18 hours out of which 2(2.32%) expired. While 15 patients received STK between 18 to 24 hours on onset of AMI out of which 3(3.48%) expired.

Type of AMI

In the LATE study (1993) 60.4% patients had Q wave MI (QMI), in the present study, a higher number of patients 87.20% had QMI. This small difference may be due to the fact study population was very small in the present study.

Pre Infarction Angina (PIA) and Associated Mortality

In the present study there were 61(35.5%) patients who had pre infarction angina. This incidence of PIA was compared with the outcome. Of the total of 172 patients in this study, there were 61 patients who had history of PIA out of which 4(6.6%) patients expired. On the contrary there were 111 patients who did not have history suggestive of PIA and there were 6(5.4%) deaths. This difference was not statistically significant (p=NS).

In Group1 there were 32(37.02%) patients who had history suggestive of PIA and out of them 4(12.5%) expired. The remaining 28 (87.5%) patients were discharged. In Group2 there were 29 (33.7%) patients who had history suggestive of PIA and all of them were discharged.

Risk Factors

- Hypertension was noticed in 36(41.86%) patients in the Group1 and in 48(55.81%) patients in the group 2.
- There were 19(22.09) and 23(26.74%) smokers in the Group1 and in the Group2 respectively.
- Hypercholesterolemia was noticed in 13 (15.11%) and 17(19.76%) patients in the Group1 and Group2 respectively.
- Diabetes was reported in 20(23.25%) and 26(30.23%) patients in the Group1 and Group2 respectively.
- There were 19(22.09%) and 20(23.25%) patients in Group1 and Group2 respectively who had hypertriglyceridemia.
- Obesity was noticed in 39(45.34%) and 33(38.37%) patients in the Group1 and Group2 respectively.
- There were only 3(13.00%) patients who had history of oral contraceptive intake in both groups, of which 1(33.3%) expired in the Group1 where as there was no mortality observed in Group2.

- There were 8(34.8%) and 2(12.5%) patients in Group1 and in Group2 respectively who were post menopausal, of which 1(12.5%) expired in Group1 and there was no mortality observed in Group2. There were 15(65.2%) post menopausal patients in Group1 and 13(87.5%) post menopausal patients in Group2, of which 2(13.3%) expired in Group1 and there was no mortality in Group2.
- There was positive family history of coronary artery disease in 10 (11.62%) patients in Group1 and 6 (6.97%) patients in Group 2. From the above it is evident that except for obesity and family history of coronary artery disease, all other risk factors were more frequent in Group 2 as compared to Group1.

Diabetes and Sex Distribution

In the Group1 there were 2(8.7%) diabetic female patients out of which there was 1mortality. In group2 there were 6(40.0%) female diabetic patients out of which none expired. There was 21(91.3%) diabetic patients female in group1, out of which there were two mortalities. In the Group2 there were 9(60.0%) non diabetic female patients of which none expired. In Group1 there were 18(28.6%) diabetic male patients out of which none expired. In the Group2 there were 20(28.2%) male diabetic patients out of which there was 1mortality. There were 45(71.4%) diabetic male patients in Group1, out of which there were 5 mortalities in Group2 there were 51(71.8%) non diabetic male patients of which there was only 1mortality.

AMI and Diet Type Relation to Mortality

It was observed that in the Group1 there were 37(43.02%) vegetarian patients of which 3(8.1%) expired where as in the Group2 out of 36(41.9%) who were vegetarians, there was only 1 (2.8%) mortality.

Vital Signs

Topol *et al.,* (1992) in their study TAMI-6 reported mean pulse and heart rate 79 per minute. A similar observation was made by LATE study group (1993) where the mean pulse and heart rate was 79 per minute. EMERAS study group (1993) found that the mean pulse and heart rate was 74.9 per minute. In the present study mean pulse rate and heart rate was 88.94 per minute which is more than that of the previous studies conducted. TAMI-6 study conducted in the year 1992 found that the mean systolic blood pressure was 123 +/- 23, in the LATE study group (1993) the mean systolic blood pressure was 139+/-24. Mean systolic blood pressure in the present study was found to be 123.20 +/- 27.73. There was no significant difference among the various studies. The diastolic blood pressure in the LATE study group (1993), was 84+/-14 where as in the present study the mean diastolic blood pressure was found to be 80.6+/-22.90. There was no significant difference when both the studies were compared.

Comparative Study of Blood Pressure

	Year	No of Patients	SBP(mm/hg)	DBP (mm/hg)
TAMI-6	1992	197	129+/-23	NA
LATE	1993	5711	139+/-24	84+/-14
Present Study	1997	172	122+/-27.74	80.6+/-22.90

Complications after AMI

In the Group1 there were 24 Patients who had post myocardial infarction congestive cardiac failure, and 14 patients had post myocardial infarction arrhythmias. These 14 patients presented as follows-

Table of Arrhythmias

Arrhythmia Type	No of Patients
Ventricular Bigemini	1
Left Anterior Hemiblock	2
Right Bundle Branch Block	2
Mobitz type ii AV Block	1
Ventricular Fibrillation	1
Pericarditis with LBBB and LV Clot	1
Post Infarction Angina	2
Renal Failure	1

Mortality

In Group1, 78(90.69%) patients were discharged and 8(9.30%) expired. In Group 2, 84(97.67%) patients were discharged and only 2 (2.32%) expired. Results of this study were consistent with the previous trials as listed below in table3

Table of Comparison of Mortality in Different Studies

	Year	No of Patients	Mortality (%)
TAMI6	1992	197	9.1
LATE	1993	5711	19
EMERAS	1993	4534	11.8
Present Study	1997	172	9.30

Reasons for Delayed Presentation

The various reasons which were found to be the cause of delayed presentation to the hospital after the onset of AMI are stipulated as below.

1 Inability to recognize chest pain as of cardiac in origin – 44 (51.16%) patients.

2 Lack of transport facility – 9(10.46%) patients presented late because suitable transport facility was not available at the time of onset of symptoms of AMI.

3 Unwillingness to go to the hospital was the reason for delayed presentation in 29(33.72%) patients.

4 There were 14 (16.27%) patients who presented late as they tried self medication with antacids and analgesics.

5 62(72.09%) patients presented late because they were referred late by the town practitioner.

6 There were 19(22.09%) patients who presented late because there was a delay in obtaining the ECG by the referring doctor.

7 An important cause for not presenting early to the hospital was misinterpretation of the ECG by the referring doctor and this caused delay in 40(46.51%) patients.

8 There were 35(40.69%) who were unable to afford the treatment and hence did not go to the hospital till their health deteriorated.

9 Low educational standards was cause of late presentation in 8(9.30%) patients.

10 90.70% of the patients (8 in no) who presented late were unaware of the thrombolytic therapy as a form of treatment for AMI.

11 There were 21(24.41%) patients who presented late due to lack of diagnostic aid for AMI in the peripheral centers.

12 One (1.16%) pts was afraid of IV medication so this caused him to delay going to the hospital.

13 There were 2 (2.32%) patients who presented late because their ECG's showed delayed changes suggestive of AMI.

14 1(1.16%) patient knew he had AMI but did not seek medication knowingly.

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