Original Research Article

Study of clinical outcome in STEMI patients thrombolysed with non-fibrin specific streptokinase at a teaching hospital

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Abstract

Background: The Fibrinolytic agents currently approved for treating patients with STEMI include streptokinase, alteplase, reteplase and tenecteplase. In present study, we aimed to study feasibility and efficacy of the pharmacoinvasive approach for AMI using streptokinase as the thrombolytic agent. **Material and Methods:** Present study was hospital based, prospective, observational study, conducted in patients with Myocardial Infarction with ST-segment elevation who presented within 12 hours after the onset of symptoms and where primary PCI could not be done, were treated with Streptokinase if not contraindicated, along with other medicines as per ACC/AHA STEMI guidelines. **Study Duration**: From January 2018 to December 2019 at Bharati Vidyapeeth Medical College And Hospital, Sangli. **Results:** In present study 52 patients were studied, mean age was 52.13 ± 9.98 years. Most of the patients were in from 51-60 years of age group (34.6%), followed by 41-50 years of age group (28.8%). In present study male to female ratio was 4.2:1. Of the 52 patients enrolled in the study, 29 patients had acute anterior wall myocardial infarction and 23 had acute inferior wall myocardial infarction. Among those with acute inferior wall myocardial infarction, 18 patients had >2mm ST segment depression in anterior leads and 10 patients had >1mm ST segment elevation in V_4R. Time from symptom onset to administration of Streptokinase ranged from 30 minutes to 11 hours (Mean 4.47±2.73 hours). Majority of the patients (44.2%) were thrombolysed between 2hrs-4hrs. Cardiac catheterization was performed in all patients at a median of 9.23 hours after fibrinolysis with Streptokinase. A follow-up evaluation at 30 days and 6 month was completed for all the patients. The overall primary end point occurred in 26.9% of the patients. Death occurred in 5.8%, Reinfarction in 5.8%, recurrent ischemia in 3.8%, Congestive heart failure in 7.7% and Cardiogenic shock was seen in 5.8% of the cases. Death and reinfarction at 6 months occurred in 7.7% and 5.8% of the patients respectively. **Conclusion:** The non-fibrin specific Streptokinase has a place in Pharmacoinvasive strategy particularly where contemporary fibrin specific agents (alteplases) are being rendered out of reach of common people due to their exorbitant cost.

Keywords: PCI, fibrinolysis, STEMI, streptokinase.

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INTRODUCTION

Coronary artery disease (CAD) is epidemic in India and one of the major cause of disease- burden and death. A total of nearly 64 million cases of cardiovascular diseases are likely in the year 2015, of which nearly 61 million would be CAD cases (the remaining would include stroke, rheumatic heart disease and congenital heart diseases). Deaths from this group of diseases are likely to amount to be a staggering 3.4 million.[1] Pharmacological reperfusion therapy has been a major advance in the treatment of STEMI. The knowledge of thrombotic occlusion of the infarct related artery, spurred advances in

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pharmacotherapy in the form of thrombolytic agents. Though not yet the final answer, Thrombolytic therapy remains the cornerstone for treating acute myocardial infarction the world over. The Fibrinolytic agents currently approved for treating patients with STEMI include streptokinase, alteplase, reteplase and tenecteplase.[2] For developing and underdeveloped countries, streptokinase remains the main agent for thrombolysis in these countries. It is well known that the best available thrombolytic gives about 50-60 % patency of the infarct related artery. Thus almost 50 % of post thrombolysis patients are left with incomplete revascularisation. The TRANSFER-AMI[3] trial was a landmark in testing this hypothesis, and showed statistically significant benefits in the study patients, thrombolysed with Tenecteplase followed by PCI. In present study, we aimed to study feasibility and efficacy of the pharmacoinvasive approach for AMI using streptokinase as the thrombolytic agent.

MATERIAL AND METHODS

Present study was hospital based, prospective, observational study, conducted in Department of Cardiology, From January 2018 to December 2019 at Bharati Vidyapeeth Medical College And Hospital, Sangli, Maharashtra, India. All Patients with Myocardial Infarction with ST-segment elevation who presented within 12 hours after the onset of symptoms and where primary PCI could not be done, were treated with Streptokinase if not contraindicated, along with other medicines as per ACC/AHA STEMI guidelines. Patients were eligible for inclusion in the study either if they had ST-segment elevation of 2 mm or more in two anterior leads or if they had ST-segment elevation of 1 mm or more in two inferior leads and at least one of the following high-risk characteristics: systolic blood pressure of less than 100 mm Hg, heart rate of more than 100 bpm, Killip class II or III, ST-segment depression of 2 mm or more in the anterior leads, or ST-segment elevation of 1 mm or more in right-sided lead V_4(V_4R), which is indicative of Right ventricular involvement.

Exclusion criteria included cardiogenic shock before randomization, PCI within the previous month, previous coronary- artery bypass surgery, and the availability of primary PCI with an anticipated door-to-balloon time of less than 60 minutes.

Study was explained to patients/relatives and written informed consent was taken for participation. Proper study approval was taken from institutional ethical committee. All patients received Streptokinase, Aspirin, Clopidogrel and Enoxaparin in the emergency department. Cardiac catheterisation was done in all the patients within 3-24 hours of Fibrinolysis, regardless of coronary flow. PCI was performed when persistent occlusion or substantial stenosis of the infarct-related artery, either stenosis of 70% or more of the diameter of the artery or stenosis of 50 to 70% with thrombus, ulceration, or spontaneous dissection was present. Stents were implanted during PCI whenever technically possible. The protocol allowed for the use of glycoprotein IIb/IIIa antagonists during PCI and for 12 hours (if Abciximab was the agent used) or 18 hours (if Eptifibatide was used) after PCI at the discretion of the interventional cardiologist. The primary end point of the study at 30 days was the combined incidence of death, reinfarction (after 18 hours, recurrent ST-segment elevation and recurrent chest pain lasting at least 30 minutes), recurrent ischemia (chest pain lasting 5 minutes or longer associated with ST- segment or T-wave changes), CHF or cardiogenic shock. Secondary end points at 6 months included death and reinfarction. The incidence of bleeding complications, was classified with the use of the Thrombolysis in Myocardial Infarction (TIMI) severity scales. TIMI major bleed - any intracranial bleeding/ Clinically overt signs of haemorrhage associated with a drop in haemoglobin of >5 g/dL/ Fatal bleeding (bleeding that directly results in death within 7 d) and TIMI minor bleed - clinically overt (including imaging), resulting in haemoglobin drop of 3 to < 5 g/Dl. Descriptive and inferential statistical analysis has been carried out in the present study. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study 52 patients were studied, mean age was 52.13 ± 9.98 years. Most of the patients were in from 51-60 years of age group (34.6%), followed by 41-50 years of age group (28.8%). In present study male to female ratio was 4.2:1. Of the 52 patients enrolled in the study, 29 patients had acute anterior wall myocardial infarction and 23 had acute inferior wall myocardial infarction. Among those with acute inferior wall myocardial infarction, 18 patients had >2mm ST segment depression in anterior leads and 10 patients had >1mm ST segment elevation in V4R. All the patients enrolled were thrombolysed with non-fibrin specific agent Streptokinase at a median of 4.47 hours after symptom onset. Time from symptom onset to administration of Streptokinase ranged from 30 minutes to 11 hours (Mean 4.47±2.73 hours). Majority of the patients (44.2%) were thrombolysed between 2hrs-4hrs.

Table 1: General characteristics

General characteristics	Number of patients	%
Age in years		
31-40	9	17.3
41-50	15	28.8
51-60	18	34.6
61-70	9	17.3
>70	1	1.9
Gender		
Male	42	80.8
Female	10	19.2
ST ELEVATION		
Anterior Leads	29	55.8
≥2-mm ST depression in the anterior leads	18	34.6
>1mm ST elevation in V4R	10	19.2
Inferior Leads	23	44.2
Time from symptom onset to administration of Streptokinase		
<2	7	13.5
2-4	23	44.2
4-6	11	21.2
6-10	9	17.3
>10	2	3.8

Cardiac catheterization was performed in all patients at a median of 9.23 hours after fibrinolysis with Streptokinase. LAD was the infarct related artery in 29 patients, LCx in 3 and RCA in 20 patients. PCI with stent implantation was performed in 37 (71.2%) patients at the time of Cardiac catheterization. PCI with stent implantation was performed in 37 (71.2%) patients at the time of Cardiac catheterization. Bare metal stent was put in 51.9% of the cases and Drug eluting stent in19.2%. Thrombectomy was done in 23 patients (44.2%). 17.3% of the patients were referred for CABG after cardiac catheterization as the coronary anatomy was not suitable for PCI. 11.5% of the patients did not require PCI and stenting as the infarct related coronary artery was found to be recanalized. Glycoprotein IIb/IIIa antagonists were administered in 38.5% of the patients.

Table 2: treatment characteristics

Treatment characteristics	Number of patients (n=52)	%
Time to catheterization after streptokinase (hrs.)		
3 - 12 hours	47	90.3
12.5 - 24 hours	5	9.6
Mean ± SD	9.23±2.12 hours	
Cardiac catheterization		
Infarct- related coronary artery		
LAD	29	55.8
LCx	3	5.8
RCA	20	38.5
Baseline TIMI flow		
0	10	19.2
1	16	30.8
2	18	34.6
3	8	15.4
Thrombectomy done	23	44.2
Stent implanted		
BMS	27	51.9
DES	10	19.2
N	15	28.8
Additional treatment		
CABG	9	17.3
Gp IIb/IIIa inhibitor use	20	38.5

A follow-up evaluation at 30 days and 6 month was completed for all the patients. The overall primary end point occurred in 26.9% of the patients. Death occurred in 5.8%, Reinfarction in 5.8%, recurrent ischemia in 3.8%, Congestive heart failure in 7.7% and Cardiogenic shock was seen in 5.8% of the cases. Death and reinfarction at 6 months occurred in 7.7% and 5.8% of the patients respectively.

Table 3: end points

Efficacy end points	Number of patients (n=52)	%
Primary	14	26.9
Death	3	5.8
Reinfarction	3	5.8
Death and Reinfarction	2	3.8
Recurrent Ischemia	2	3.8
Death and Reinfarction and Recurrent Ischemia	2	3.8
CHF	4	7.7
Cardiogenic Shock	3	5.8
Secondary	7	13.5
Death	4	7.7
Reinfarction	3	5.8

Hemodynamic evaluation was done on the basis of Killip class. 44.2% of the patients were in Killip class I. 46.2% were in Killip class II and 9.6% were in Killip class III. Killip class IV (Cardiogenic Shock) patients were excluded from the study. Risk factors studied included- Smoking (57.7%), Hypertension (34.6%), dyslipidemia (59.6%) and Diabetes (50%). We compared various clinical variables like age (years), gender (male/female), Killip class (I/II/III), comorbid conditions (smoking, HTN, dyslipidaemia, diabetes), treatment (aspirin, clopidogrel, B-Blocker, ACEI, statins, enoxaparin), access (femoral/radial), time from symptom onset to administration of Streptokinase, time to catheterization after streptokinase (hrs.), baseline TIMI flow between patients with and without primary end points and all clinical variables were comparable between two groups and difference was not significant statistically.

Table 4: Correlation of clinical variables according to Primary efficacy end points

Clinical variables	Primary efficacy end point		P value
	Absent (n=38)	Present (n=14)	
Age in years	51.42±10.29	54.07±9.13	0.401
Male	31(81.6%)	11(78.6%)	
Female	7(18.4%)	3(21.4%)	1.000
Killip class			
Class I	19(50%)	4(28.6%)	
Class II	17(44.7%)	7(50%)	
Class III	2(5.3%)	3(21.4%)	0.132
Comorbid condition			
Smoking	22(57.9%)	8(57.1%)	1.000
HTN	11(28.9%)	7(50%)	0.197
Dyslipidaemia	25(65.8%)	6(42.9%)	0.135
Diabetes	18(47.4%)	8(57.1%)	0.532
Treatment			
Aspirin	38(100%)	14(100%)	1.000
Clopidogrel	38(100%)	14(100%)	1.000
B-Blocker	32(84.2%)	11(78.6%)	0.688
ACEI	36(94.7%)	11(78.6%)	0.114
Statins	38(100%)	14(100%)	1.000
Enoxaparin	34(89.5%)	14(100%)	1.000
Access			
Femoral	12(31.6%)	6(42.9%)	
Radial	26(68.4%)	8(57.1%)	0.519
Time from symptom onset to administration of Streptokinase	4.44±2.69	4.54±2.95	0.919
Time to catheterization after streptokinase (hrs.)	9.14±2.04	9.46±2.38	0.635
Baseline TIMI flow	1.61±0.95	1.07±0.99	0.081

DISCUSSION

The Pharmacoinvasive therapy in this paper in particular, refers to the technique whereby there is a time elapse of 3-24 hours between Thrombolysis (pharmaco) and PCI (invasive) when using fibrin non-specific thrombolytic agent-Streptokinase. This approach of pharmaco invasive strategy increases the speed of myocardial reperfusion by pharmacologically opening the infarct-related artery rapidly, followed by PCI to ensure sustained and more complete reperfusion thus resulting in less myocardial damage and consequently a decrease in clinical events.[4] Since most of the reocclusion and reinfarction occur in the initial 24 hours, the ESC guidelines now recommend routine post thrombolytic PCI between 3 and 24 hours.

Fibrinolytic Therapy Trial[5] compared the outcomes of patients undergoing Fibrinolytic therapy and those of controls demonstrated statistically significant absolute reductions in 35-day mortality rates of approximately 30 per 1000 for patients who arrived at the hospital within 6 hours of the onset of symptoms and of approximately 20 per 1000 for patients who arrived 7 to 12 hours after the onset of symptoms. Benefit was observed among patients with ST-segment elevation or left bundle branch block (LBBB) at the time of presentation, irrespective of age, sex, blood pressure, heart rate, or a history of myocardial infarction (MI) or diabetes. The greatest benefit was observed among patients with LBBB or anterior STEMI. Fibrinolytic therapy is currently indicated, in the absence of contraindications (for patients with STEMI who have experienced symptom onset within the previous 12 hours and in whom electrocardiography (ECG) demonstrates ST-segment elevation of more than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads, or new or presumably new LBBB. Current guidelines recommend primary PCI for patients who can undergo coronary intervention within 90 minutes after presentation.[6] Present study was not adequately powered to make a concrete statement on the mortality benefit of using non-fibrin specific agent Streptokinase as fibrinolytic agent. There were 3(5.8%) deaths at 30 days, and 4(7.7%) at 6 months, but still these rates did not differ significantly from the early PCI arm of TRANSFER AMI trial[3] (death occurred in 4.5% and 5.7% of the cases at 30 days and 6 months respectively), where a more fibrin specific agent Tenecteplase was used for fibrinolysis. Death at the end of 30 days and 6 months were 3% and 5.6% in CARESS- IN AMI trial[7], 2.4% and 3.6% in GRACIA-1 trial[8], 2.32% and 3.48% in CAPITAL AMI trial[9], 2.23% and 2.23% in NORDISTEMI trial[10] respectively. All these contemporary Pharmacoinvasive trials have used more fibrin specific agent either in the form of Tenecteplase, Reteplase or Alteplase as a fibrinolytic agent in contrary to our study, where Streptokinase (non- fibrin specific) was used. In a cumulative meta-analysis[11] of all the Pharmacoinvasive trial, there were 49 deaths (3.3%) in the early invasive group, re- infarction in 2.6%, the combined endpoint of death/reinfarction in 5.6% and recurrent ischemia in 1.9% of the patients at the end of 30 days. Clinical end points at 6 months were, reinfarction in 3.9% and the combined endpoint of death/reinfarction in 8.6% of the patients. Death occurred in 5.8%, Reinfarction in 5.8%, recurrent ischemia in 3.8%, Congestive heart failure in 7.7% and Cardiogenic shock was seen in 5.8% of the cases at 30 days. Death and reinfarction at 6 months occurred in 7.7% and 5.8% of the patients respectively. The overall primary end point a composite of death, reinfarction, recurrent ischemia, congestive heart failure, or cardiogenic shock at 30 days occurred in 26.9% in our trial, 24% in WEST study[12], 11% in TRASFER-AMI[3] study and 10.7% in CARESS-in-AMI trial[7]. The higher primary end point in our study was mainly driven by a slightly higher incidence of death, re-infarction, congestive heart failure and cardiogenic shock. In fact 3 of our patient who met the criteria of cardiogenic shock at 30 days, expired. The higher overall primary end point and its individual component in our study could be attributed to the fact that Streptokinase as a fibrinolytic agent in Pharmacoinvasive strategy has certain limitations. It is non-fibrin specific. In country like India and more so in a rural setup like our hospital, where most of our patients come from financially challenged background and cannot afford costly fibrin specific agents. In such a situation Streptokinase still holds good and is a viable option for Pharmacoinvasive therapy next to more fibrin specific lytic agents such as Tenecteplase, which has been endorsed by ACC/AHA guidelines for the same. The main limitation of this study were non-randomization, smaller sample size and shorter duration of follow up.

CONCLUSION

Primary PCI and fibrinolysis are the 2 principal methods in STEMI to decrease mortality and morbidity. The non-fibrin specific Streptokinase has a place in Pharmacoinvasive strategy particularly where contemporary fibrin specific agents (alteplases) are being rendered out of reach of common people due to their exorbitant cost.

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