ORIGINAL ARTICLE

EFFICACY OF LATE THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT: Efforts are being made to give thrombolytic therapy as early as possible after acute myocardial infarction (AMI). However, more than 30% of AMI patients present to hospital 6 hours after the onset of their first symptom i.e., later than the usual time window for administration of thrombolytic therapy. Thus, extension of this time window to patient coming up to 24 hours after the symptom onset will make such therapy available to more patients. **OBJECTIVES:** To assess the efficacy of thrombolytic therapy with IV streptokinase after 6 to 24 hours of the onset of chest pain in acute AMI patients in terms of: Immediate effect on symptom relief and ECG changes of reperfusion. Effect on mortality in hospital; at one month, 6 months and one year follow-up. To compare the above data with patients who were thrombolyzed within 6 hours from pain onset and patients who were not thrombolyzed within 24 hours from onset of pain.
KEYWORDS: Acute myocardial infarction; Thrombolytic therapy.

INTRODUCTION: Coronary heart disease is increasing in prevalence and is the leading cause of death and disability worldwide.

At the beginning of the 20th century cardiovascular disease accounted for less than 10% of all deaths worldwide. At the beginning of the 21st century, they accounted for nearly half of all deaths in the developed world and 25% in the developing world. By 2020, it is predicted that the disease will claim 25 million lives annually and the coronary heart disease (CHD) will surpass infectious diseases as the world's number one cause of death and disability.[1]

Clinical coronary artery disease (CAD) in Indians occur at a younger age, is more severe and extensive, and follows a malignant course. This has been documented in studies of Indian immigrants. Cross-sectional studies in India were also documented a several fold higher prevalence of CAD than in industrialized nations. By the year 2020, the burden of atherothrombotic cardiovascular disease in India will surpass that in other regions of the world. The mortality attributable to cardiovascular disease in India is expected to rise by 103 percent in men and by 90 percent in women from 1985 to 2015.[2]

Clinical manifest CAD may present as stable angina, acute coronary syndrome or sudden cardiac death. Acute coronary syndromes encompass patients who have evidence of myonecrosis, or are felt to be at high risk of myonecrosis in the immediate future and thus include patients with unstable angina, non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI).[3]

Acute STEMI affects 30% to 50% of patients presenting with an acute coronary syndrome (ACS) and requires immediate reperfusion therapy,[4] whether accomplished by mechanical or pharmacologic means. Early coronary artery reperfusion salvages ischemic myocardium, improves left ventricular function and prolongs patient survival.[5]

Intravenous thrombolytic therapy has remained the mainstay of reperfusion therapy because of its universal and rapid availability. Thrombolytic therapy of evolving myocardial infarction is based on the concept that severely ischemic myocardium can be salvaged by restoring blood supply to reversibly injured tissue. It has been demonstrated that the earlier reperfusion is achieved the more likely that the myocardial damage can be limited and mortality reduced.[6]

The potential value of the late administration of thrombolytic therapy in patients with acute myocardial infarction is highly controversial. A meta-analysis of intravenous thrombolytic trials with registries has indicated that more than 30% of patients with myocardial infarction present for medical care between 6 and 24 hours after symptom onset.[7]

In ISIS-2 trial, a 22% reduction in 5 weeks vascular mortality was evident in the 6477 patients treated 7 to 24 hours after symptom onset ($p<0.05$, two tailed t-test).[7]

The mechanism other than left ventricular salvage has been postulated to account for the apparently salutary effect of late reperfusion. These include a reduction in the formation of left ventricular aneurysms, a reduction in ventricular electrical instability and potentially lethal ventricular arrhythmias, a reduction in the incidence of left ventricular thrombus formation, and the provision of a conduit for collateral flow in the event of subsequent contralateral vessel occlusion.[7]

The value of late thrombolysis even though uncertain, the issue is important. As extension of time window for thrombolytic therapy would make such therapy available to more patients.

Hence, this study is undertaken to evaluate the potential value of delayed thrombolysis on left ventricular function and overall mortality in acute myocardial infarction.

METHOD: A total of 100 consecutive patients at their first episode of AMI admitted within 24 hours from the onset of chest pain were included in the study. Once diagnosis of STEMI made and thrombolytic therapy was given, all patients were categorized into 4 groups. First 3 groups received thrombolytic therapy with 1.5 million IU of streptokinase in 100 ml of normal saline over 45 minutes, categorized on duration from onset of chest pain to administration of thrombolytic therapy and the fourth group included non-thrombolyzed patients.

Group-I	0 to 6 hours (47patients) – 47%
Group-II	7 to 12 hours (24 patients) – 24%
Group-III	13 to 24 hours (11 patients) – 11%
Group-IV	Non-thrombolyzed group (18 patients) – 18%

Thus, 35 patients (35%) belonged to late thrombolyzed group (7-24 hours).

All the patients were followed up for in-hospital complications and mortality, left ventricular function was assessed by 2D Echo before discharge. Patients who survived initial hospitalization were followed up for mortality at 1 month, 6 months and 1 year during the study period.

RESULTS: Total 100 consecutive patients at their first episode of myocardial infarction, admitted to ICCU within 24 hours from onset of chest pain were studied.

Duration (Hours)	No. of Cases	Percentage
0 – 6 hrs	55	55
7 – 12 hrs	28	28
13 – 24 hrs	17	17
Total	**100**	**100**

Table 1: Distribution of cases according to duration from chest pain to hospital admission in hours

Out of 100 patients, 55 patients (55%) presented to the hospital <6 hours of chest pain, 28 patients (28%) between 7-12 hours and 17 patients (17%) within 13-24 hours from onset of chest pain. After thrombolysis, all the patients were grouped according to the duration from the onset of chest pain to administration of thrombolytic agent into 0-6 hours, 7-12 hours and 13-24 hours and non-thrombolyzed group.

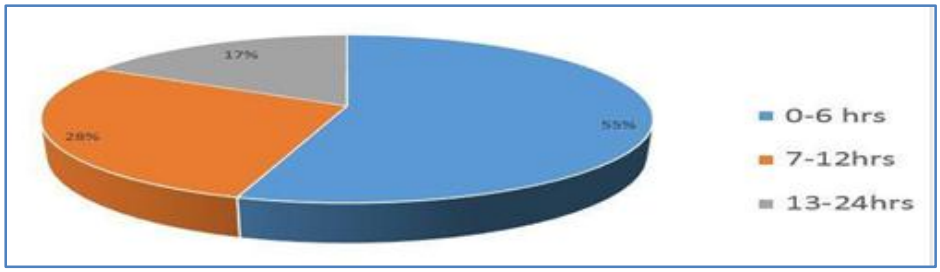

Fig. 1: Distribution of cases according to duration from chest pain to hospital admission in hours

Out of 100 patients, 82 patients (82%) received thrombolytic therapy and 18 patients (18%) did not receive thrombolytic therapy.

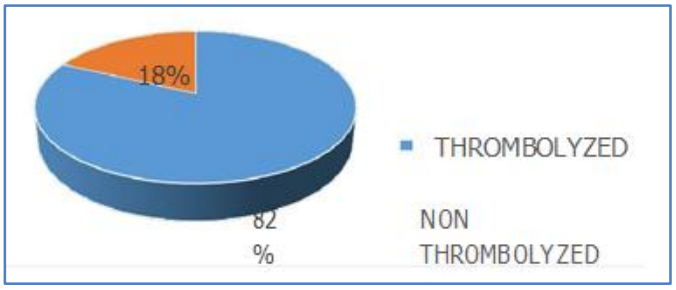

Fig. 2: Distribution of cases according to thrombolytic therapy

Out of 82 patient who received thrombolytic therapy, 47 patient (47%) were thrombolyzed between 0-6 hours from onset of chest pain i.e., early thrombolyzed, 24 patients (24%) between 7-12 hours, 11 patients (11%) between 13-24 hours from pain onset. Thus 35 patients (35%) were late thrombolyzed i.e., 7-24 hours.

18 patients belonged to the non-thrombolyzed group out of total 100 patients (8 admitted within 0-6 hours, 4 patients between 7-12 hours and 6 patients within 13-24 hours from onset of chest pain).

Figure-3: Distribution of cases according to duration from onset of chest pain to institution of thrombolytic therapy in hours.

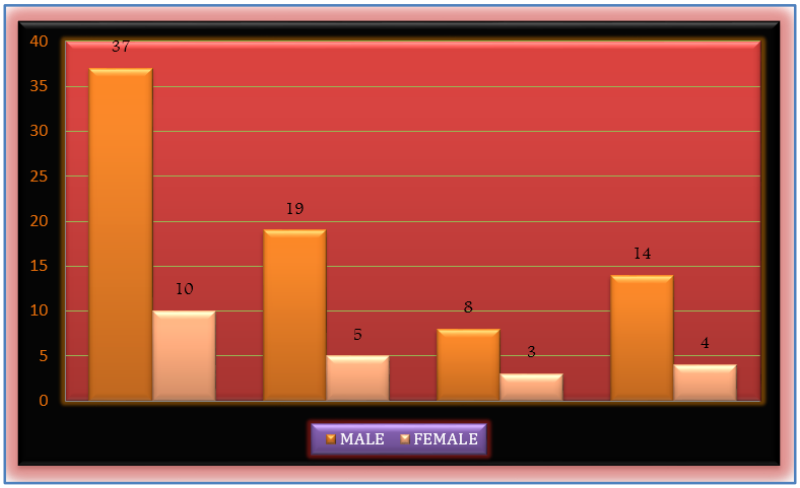

Fig. 3

Maximum number of AMI cases occurred in the age group of 46-55 years (30%) followed by 36-45 years (25%). There were 8 patients (8%) above 75 years in the present study.

In the present study incidence of AMI was more common in males – 78 patients (78%) as compared to 22 female patients (22%).

Figure 4: Distribution of cases according to duration from onset of chest pain to thrombolytic therapy and sex.

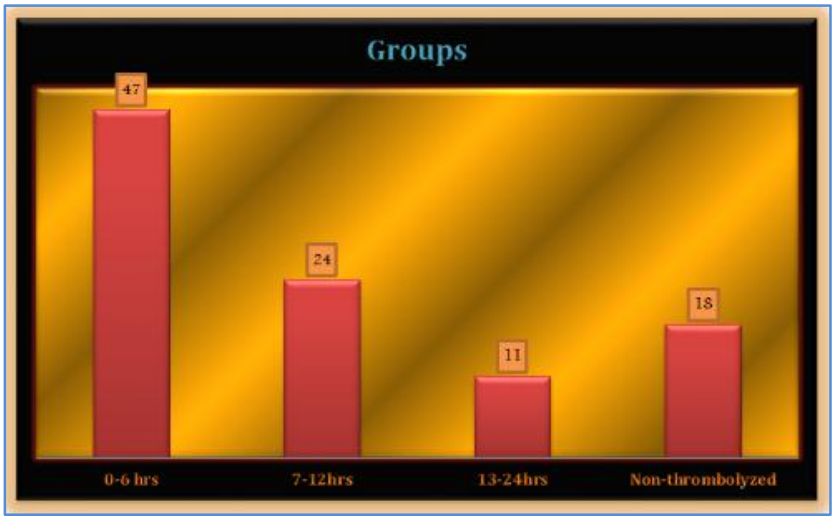

Fig. 4

Smoking was the most common risk factor and was present in 69% of patients, followed by dyslipidemia in 39%, diabetes mellitus in 20%, and obesity in 18% and hypertension in 11% of AMI patients. All the female patients (100%) were in the postmenopausal status.

Out of 100 patients, anterior wall MI was present in 63 patients (63%), inferior wall MI in 30 patients (30%), inferior wall with right ventricular MI in 6 patients (6%) and 1 patient (1%) had global MI.

Group	Features of Reperfusion – Decreased chest pain					
	Yes		No		Total	
	No.	Percent	No.	Percent	No.	Percent
Thrombolyzed (n=82)						
0 – 6 hrs	31	65.96	16	34.04	47	100.00
7 – 12 hrs	11	45.83	13	54.17	24	100.00
13 – 24 hrs	4	36.36	7	63.64	11	100.00
Non-thrombolyzed (n=18)	4	22.22	14	77.78	18	100.00
Total	**50**	**50**	**50**	**50**	**100**	**100.00**

Table 2: Distribution of cases according to decrease in chest pain after treatment

Immediate symptomatic reduction in chest pain is seen in 31 patients (65.96%) of 0-6 hours group, 11 patients (45.83%) of 7-12 hours group and 4 patients (36.36%) of 13-24 hours group. In non-thrombolyzed group 4 patients (22.22%) had decrease in chest pain with routine coronary care treatment.

Group	Features of Reperfusion - Resolution of ST Elevation					
	Yes		No		Total	
	No.	Percent	No.	Percent	No.	Percent
Thrombolyzed (n=82)						
0 – 6 hrs	23	48.94	24	51.06	47	100.00
7 – 12 hrs	8	33.33	16	66.67	24	100.00
13 – 24 hrs	2	18.18	9	81.82	11	100.00
Non-thrombolyzed (n=18)	3	16.67	15	83.33	18	100.00
Total	**36**	**36**	**64**	**64**	**100**	**100.00**

Table 3: Distribution of cases according to resolution of ST segment elevation after treatment

Rapid resolution of ST elevation after treatment was observed in 23 patients (48.94%) of 0-6 hours group, 8 patients (33.33%) of 7-12 hours and 2 patients (18.18%) in 13-24 hours group. Whereas in the non-thrombolyzed group, ST elevation resolution was observed only in 3 patients (16.67%).

Therapy	No. of Cases	Percentage
Thrombolyzed	11	13.41
Non-thrombolyzed	4	22.22
Total	**15**	**15**

Table 4: Distribution of cases according to thrombolytic therapy and in-hospital mortality

Out of total 100 patients, 15 (15%) patients died in the hospital. There were 11 deaths (13.41%) in thrombolyzed group and 4 (22.22%) deaths in non thrombolyzed groups.

There were 7 deaths (14.89%) in 0-6 hours group. 1 (4.16%) in 7-12 hours, 3 (27.27%) in 13-24 hours and 4 (22.22%) in non-thrombolyzed group. When mortality in 7-24 hours group is combined (late group), there were 4 deaths (11.42%).

AT 1 MONTH FOLLOW-UP: Out of 85 patients who survived initial hospitalization follow-up was done for 70 patients i.e., 33 patients (7 lost) in 0-6 hours group, 20 patients (3 lost) in 7-12 hours group, 7 patients (1 lost) in 13-24 hours group and 10 patients (4 lost) in non-thrombolyzed group and following are the observations.

At 1 month, there was 1 death in 0-6 hours group, 1 death in 13-24 hours group and 1 in non-thrombolyzed group.

AT 6 MONTHS FOLLOW-UP: Out of 67 patients who came for 1 month follow-up, 57 patients were eligible for 6 months follow-up within the study period. Follow-up was done for 50 patients 24 patients (3 lost) in 0-6 hours, 15 (2 lost) in 7-12 hours, 4 (1 lost) in 13-24 hours, 7 patients (1 lost) in non-thrombolyzed group. Following are the results of the observations.

Out of 50 people followed-up, 1 patient had died in 7-12 hours and 2 patients in non-thrombolyzed group by 6 months.

AT 1 YEAR FOLLOW-UP: Out of 47 patients who came for 6 months follow-up, 30 cases were eligible for 1 year follow-up. Follow up was done for 30 cases. Following are the observations noted

There was 1 death in 7-12 hours group at 1 year of follow-up.

DISCUSSION: A hospital based study was done to know whether thrombolytic therapy administered late (7-24 hours of chest pain) has any benefit over mortality and left ventricular function at in hospital, at 1 month, 6 months and 1 year follow-up. This late thrombolyzed patients were compared with early thrombolyzed (0-6 hours) and non-thrombolyzed group.

In the study done by Gurwitz et al[1] 40% of the patients presented to the hospital after 6 hours of symptom onset.

In the present study, 55 patients (55%) presented <6 hours of symptoms as compared to 45 patients (45%) who presented after 6 hours of symptom onset.

In our study, the incidence of AMI was maximum in 46 to 55 years age group i.e., 30.8%,

followed by 36-45 years age group i.e., 25%.

David WM Muller and Eric J Topol in their meta-analysis of intravenous thrombolytic trial has shown that 10%-27% of AMI patients are >75 years old. In the present study 8% of the patients were >75 years old[7].

In the study conducted by Cordioli E et al[8] 62% of patients received thrombolytic therapy and 38% did not receive thrombolytic therapy. In our study, 82% received thrombolytic therapy and 18% were non-thrombolyzed.

Decades of observational studies have verified excess MI risk in men compared with women. In Kanitz et al[9] study, 81% were males and 19% were females.

In the present study 78% of acute myocardial infarction patients were male and 22% were female. Smoking accelerates atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction and death. In Tanajura et al[10] study, the prevalence of smoking was 81%.

A wealth of epidemiologic data support a relationship between hypertension and atherosclerotic heart disease, more recent studies also show a reduction in CHD, risk by antihypertensive therapy. In Tanajura et al[10] study, the prevalence of hypertension was 22%.

Abnormalities in plasma lipoprotein and derangements in lipid metabolism rank as the most firmly established and best understood risk factors for AMI. In Tanajura et al[10] study, the prevalence of dyslipidemia was 16%.

Diabetes mellitus is a chronic heart disease risk equivalent. Most patients with diabetes mellitus die of atherosclerosis and its complications. In Tanajara et al,[10] the prevalence of diabetes mellitus was 4%.

In the present study, the prevalence of smoking was 69% followed by dyslipidemia in 39%, diabetes mellitus in 20%, hypertension in 11%, obesity in 18% and all female patients were in postmenopausal status.

In the GISSI-I trial[11] 37% of patients had anterior wall MI, 34% had inferior wall MI. In our study, 63% had anterior wall MI, 30% had inferior wall MI.

After thrombolytic therapy rapid relief in chest pain was observed in 65.96% of 0-6 hours group, 45.83 of 7-12 hours, 36.36% in 13-24 hours group. Symptomatic relief in chest pain was seen 22.22% of non-thrombolyzed group after routine coronary care treatment. But it was not statistically significant in any of the groups.

Rapid resolution of ST-elevation was seen in 48.94% of 0-6 hours group, 33.33%, 18.18% and 16.67% of 7-12 hours, 13-24 hours and non-thrombolyzed group respectively, but was not statistically significant.

Even though there was no statistically significant difference in chest pain relief and ST segment resolution in any of the groups, it was observed that percentage of relief of symptom and resolution of ST-segment reduced as the time prolonged and was less in non-thrombolyzed group.

In the present study, in hospital mortality was 14.89% for 0-6 hours group, 4.16% for 7-12 hours group, 27.27% for 13-24 hours, 11.42% for combined 7-24 hours group and 22.22% for non-thrombolyzed group.

The TIMI-I trial in which 290 patients admitted within 7 hours after onset of acute myocardial infarction were randomly assigned to IV streptokinase or rt-PA, ejection fraction did not change significantly from before treatment to before discharge in either treatment group.[12]

At 1 month, 70 patients were followed up out of 85 patients who survived initial hospitalization i.e., 33 patients in 0-6 hours, 20 patients in 7-12 hours, 7 patients in 13-24 hours and 10 in non-thrombolyzed group.

There was 1 death in 0-6 hours group, 1 in 13-24 hours and 1 in non-thrombolyzed group.

In the Western Washington Intracoronary Streptokinase in Myocardial Infarction Trial, the 30 days mortality rates were 3.7% in the SK-treated group and 11.2% in the control group respectively, while radionuclide ventriculography revealed that the two groups had identical mean LVEFs.[13]

At 6 months, out of 57 patients eligible, follow up was done for 50 patients i.e., 24 patients in 0-6 hours, 15 patients in 7-12 hours, 4 patients in 13-24 hours and 7 patients in non-thrombolyzed group. At 6 months, 1 patient had died in 7-12 hours and 2 in non-thrombolyzed.

At 1 year, 30 patients, who were eligible were followed up, there was 1 mortality in 7-12 hours group.

CONCLUSION: In our study, immediate reduction in chest pain and rapid resolution of ST-segment occurred in more percentage of patients in late thrombolysis (7-24 hours) as compared to non-thrombolyzed group. But less when compared to early thrombolyzed group. In hospital mortality was less in early and late thrombolyzed group as compared to non-thrombolyzed group.

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