



FACTORS INFLUENCING THE OUTCOME OF THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Introduction: Coronary heart disease has been defined as "impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart." It is the cause of 25-30% of death in most of the industrialized countries. In India also, it is a major public health problem. It is aptly called by WHO as the modern epidemic. The increasing incidence of coronary heart disease may be a reflection of increased longevity, adoption of high-fat diet based on meats, decreased exercise, modern lifestyle, made possible by increasing affluence. The primary goal of thrombolytic therapy is rapid, complete and sustained restoration of infarct related artery blood flow. Success rate of thrombolysis and thus the overall reduction in mortality is different among different agents used. **AIMS & Objective:** To find out the overall success rate of thrombolysis in intensive care unit. Find out whether the following parameters influence the outcome of thrombolysis and determine their role in the success/ failure of thrombolysis. **Material and Methods:** Patients were included who is, presence of typical chest pain suggestive of Acute myocardial infarction along with ECG evidence Criteria for thrombolysis being 2 mm or more ST elevation in two contiguous precordial leads or 1 mm or more ST elevation in two contiguous limb leads. Time window of 12 hrs. from the onset of pain to the initiation of thrombolysis. **Drug Therapy:** All patients received streptokinase 1.5 million units in 100ml of normal, saline over 60 minutes, Aspirin was given to all patients, Use of heparin, -blockers, ACE Inhibitors was according to ICU protocols, which was in accordance with ACC/AHA recommendations. **Definition of success of thrombolysis:** Success was defined by: Clinical-complete subsidence of chest pain, Electrocardiographically-more than 50% ST resolution in a lead which showed maximum ST elevation initially. ST elevation is measured manually, 80ms after J point from isoelectric line. Preceding PR segment is taken as isoelectric line. Patients were analyzed for success of thrombolytic therapy at 90 minutes after initiation of thrombolytic therapy, applying the above mentioned criteria. Those who underwent successful thrombolysis were grouped into group A. Those with failed thrombolysis -Group B. The following parameters were analyzed: Age, Gender, Smoking status, Drinking status, Diabetes mellitus, Systemic Hypertension, Location of Myocardial Infarction, Time interval between the onset of pain and the initiation of thrombolytic therapy, Killip grading. **Results:** Patients with inferior wall myocardial infarction had a better outcome than anterior wall myocardial infarction. Alcohol, smoking and age were factors which influence the outcome, but were not statistically significant. Early thrombolysis had a better out come when compared to other predictors. Success rate was 64% in those patients thrombolysed within 4 hrs. from the onset of symptoms. Time window was found to be the most powerful factor influencing the outcome of thrombolysis in patients with acute myocardial infarction. **Conclusion:** The success rate was significantly higher with a lower Killip grading and the outcome worsened as the grading increased.

KEYWORDS : Myocardial Infarction, Streptokinase, Thrombolysis,

INTRODUCTION:

Coronary heart disease has been defined as "impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart."^[1] It is the cause of 25-30% of death is most of the industrialised countries. In India also it is a major public health problem. It is aptly called by WHO as the modern epidemic. The increasing incidence of coronary heart disease may be a reflection of increased longevity, adoption of high-fat diet based on meats, decreased exercise, modern life style, made possible by increasing affluence.

In 1892, Sir William Osler devoted a few pages in his textbook of medicine, to the discussion of acute myocardial infarction. It was the brilliant work of Herrick in 1912, who performed autopsy on Acute Myocardial Infarction patients that put forward the new concept of thrombotic occlusion of coronary artery as the cause of downstream necrosis of heart muscle.

Definitive proof for the above said concept came from angiographic studies performed during the early hours of the acute coronary event.^[2] This prompted scientists to systematically test the thrombolytic strategies to treat Acute Myocardial Infarction, opening that new era of thrombolytic therapy in Acute Myocardial Infarction. Scientists have developed many effective thrombolytic drugs like, streptokinase, recombinant tissue plasminogen activator (rt

PA), Reteplase (rPA), urokinase, APSAC (Anisoylated plasminogen streptokinase activator complex) etc. Evidence for the use of thrombolytic therapy came from large multi centre studies.^[3] GISSI and ISIS-2 confirmed reduction in mortality with the early use of streptokinase.^[4] ISAM (intravenous streptokinase in Acute Myocardial Infarction study group) also stands as a proof of efficacy of thrombolytic drugs to reduce mortality.

Success rate of thrombolysis and thus the overall reduction in mortality is different among different agents used.^[5] The GUSTO-1 trial showed a 30 day mortality of 6.3% for accelerated t-PA versus 7.4% for streptokinase with intravenous heparin.

Thrombolytic therapy has revolutionized the management of Acute Myocardial Infarction.^[6] GUSTO angiographic sub study showed a success rate of 54% at 90 minutes using IV streptokinase and Heparin. Thrombolytic therapy has been consistently proven to reduce the mortality and morbidity. In spite of this it has been recognised that thrombolytic therapy has failed in a significant population. There is lot of room for improvement. We need to identify the factors that are responsible for failure of thrombolysis.

In this background, we decided to look into our own patients who receive streptokinase for Acute Myocardial Infarction, in

the coronary care unit of Govt. General Hospital.

MATERIAL AND METHODS:

This study was conducted in SRG Hospital attached to Jhalawar Medical College in South Western Rajasthan. In this study, a total of 60 patients were studied. Their age ranged from 31 - 76 years (mean 55.01). 47 of them were males and 13 females.

Inclusion Criteria :

- Presence of typical chest pain suggestive of Acute myocardial infarction along with ECG evidence Criteria for thrombolysis being 2 mm or more ST elevation in two contiguous precordial leads or 1 mm or more ST elevation in two contiguous limb leads.
- Time window of 12 hrs. from the onset of pain to the initiation of thrombolysis.

Exclusion Criteria

- Late thrombolysis (more than 12 hrs. from the onset of pain).
- Recurrent myocardial infarction.
- Presence of bundle branch block.
- Development of pericarditis

DRUG THERAPY

All patients received streptokinase 1.5 million units in 100ml of normal saline over 60 minutes.

Aspirin was given to all patients.

Use of heparin, β -blockers, ACE Inhibitors was according to ICU protocols, which was in accordance with ACC/AHA recommendations.

Definition Of Success Of Thrombolysis :

Success Was Defined By:

- Clinical-complete subsidence of chest pain.
- Electrocardiographically-more than 50% ST resolution in a lead which showed maximum ST elevation initially. ST elevation is measured manually, 80ms after J point from isoelectric line. Preceding PR segment is taken as isoelectric line.

Patients were analyzed for success of thrombolytic therapy at 90 minutes after initiation of thrombolytic therapy, applying the above-mentioned criteria. Those who underwent successful thrombolysis were grouped into group A. Those with failed thrombolysis -Group B.

The following parameters were analyzed.

- Age
- Gender
- Smoking status
- Drinking status
- Diabetes mellitus
- Systemic Hypertension
- Location of Myocardial Infarction
- Time interval between the onset of pain and the initiation of thrombolytic therapy.
- Killip grading.

DISCUSSION:

The major finding of this study is that the location of the infarct significantly affects the outcome of thrombolysis. Those with inferior wall myocardial infarction have double chances of undergoing successful thrombolysis compared to anterior wall myocardial infarction ($P < 0.05$). This is after adjustment for all confounding variable like time window, age, smoking status, gender, diabetes and hypertension.

Similar observations were made by C. Michael Gibson, Sabina Murphy and E. Brawnwald et al. (TIMI study group). They found that TIMI grade III flow rates were lower for left

coronary and circumflex artery compared to right coronary artery after thrombolytic therapy.^[7]

The reason for this differential response will be evident when we look into the physiology of coronary circulation in right and left coronary arteries. Blood flow in right coronary artery is relatively independent of phases of cardiac cycle, being present in both systole and diastole. Whereas flow in left coronary artery is almost absent during systole and may even be reversed in conditions of heightened micro vascular tone and left ventricular hypertrophy.^[8]

The relatively thicker wall, the increased wall thickening during systolic contraction and higher intracavitary pressure of left ventricle may all produce higher intramyocardial pressure than that is observed in the thinner walled right ventricle, which is also subjected to lower filling pressures. Moreover, the extent of necrosis in anterior wall is more resulting in increased myocardial edema compared to inferior infarctions. This may further decrease the reperfusion rates in anterior infarctions. Yet another mechanism, may be, better drug delivery to right coronary artery and prolonged contact of streptokinase with the thrombus, resulting in more efficient fibrinolysis.

Alcohol And Thrombolysis:

Alcohol consumption has influenced the outcome of thrombolytic therapy in a favourable way. Univariate analysis revealed a success rate of 66.66% in drinkers versus 33.34% among non drinkers. This advantage of drinkers persisted after logistic regression analysis to remove the confounding factors, even though statistically not significant (OR = 3.16; $p = 0.06$).

Alcohol is known to reduce coronary artery disease related mortality. In a meta analysis of all experimental studies that assessed the effects of moderate alcohol intake on concentrations of HDL cholesterol, apolipoprotein A1, fibrinogen, triglycerides, and other biological markers, Eric. B. Rimm, Paige William, Kerry Fosher et al.^[9] concluded that 30g of alcohol per day would cause an estimated reduction of 24.7% in risk of coronary artery heart disease.

This better success rate observed in patients who consume alcohol may be easily explained by the effect of alcohol on hemostatic factors. In a study conducted on 631 apparently healthy male physicians, the plasmas level of tPA antigen were 10.9, 9.7, 9.1 and 8.1 ng/ml respectively in those who consumed alcohol daily, weekly, once a month and never.^[10]

Studies have shown an effect on platelets also. Alcohol reduces platelet aggregation in response to most agonists like thrombin, ADP, epinephrine and collagen.^[11]

By contrast in binge drinkers or in alcoholics after alcohol withdrawal, response to aggregation, especially that induced by thrombin, is markedly increased. This rebound phenomenon may explain ischemic strokes or sudden death known to occur after episodes of drunkenness.

Ethanol intake is also known to decrease blood fibrinogen level. Thus those who consume alcohol on a moderate basis are having better endogenous fibrinolytic response.

Influence Of Age Of The Patient Of Thrombolysis:

Patients older than 60 years are found to have a lesser success rate in univariate analysis. ($X^2 = 4.11$, OR = 2.5, $P = 0.04$). After adjustment for other parameters in logistic regression, a statistically insignificant reduction in success rate is observed.

This shows that with respect to fibrinolysis elderly people do not behave differently from younger people. This is reflected in

reduction in mortality rate among elderly after thrombolysis. In patients aged more than 75 years who were treated with Streptokinase in GISSI-2 trial, there was a reduction of 4.2 fewer deaths per 100 patients than in controls. In ISIS - 2 there was 3.3 fewer deaths per 100 patients in those over 70 years of age who were treated.^[12]

Gender:

No statistically significant difference was noticed based on gender. Woodfield - SL, Lunderberg - CF, Topol EJ et al.^[13] performed an angiographic study to find out the patency rate at 90 minutes in men versus women. At 90 minutes TIMI - 3 flow rate was 61.7% in men and 61.8% in women, which was not statistically significant. But 30 day mortality of 6.3% for accelerated t-PA versus 7.4% for streptokinase with intravenous heparin.

Thus even though females have a poor outcome after myocardial infarction, they do not behave differently to thrombolytic therapy.

Diabetes Mellitus:

In this study success rate of thrombolysis is not found to be different from non diabetic population.

Gray RP, Yudkin JS et al. found a reduction in reperfusion rates in thrombolysed diabetic patients.^[14]

Diabetes is a prothrombotic state as reflected by the increased blood levels of fibrinogen, factor VII and Wille brand factor. These changes are even more increased if diabetic people happened to be smokers.

Platelet function is also impaired in diabetics. They aggregate more readily to stimuli like ADP and collagen. Glycation of membrane proteins due to chronic exposure to high blood glucose levels^[15], change in fluidity of platelet membrane brought out by high concentration of cholesterol and triglycerides are the proposed mechanisms for these abnormalities.

On the other hand, patients with type II diabetes have profound suppression of fibrinolysis. Plasminogen activator inhibitor - I levels are high in type II diabetic people which is responsible for this effect.

Nevertheless, thrombolytic therapy should be administered to diabetics with Acute Myocardial Infarction, because for every 100 diabetic patients treated with thrombolytic drugs four lives are saved.

Preinfarction Angina:

Felicita Andreotti; Vincenzo P et al. had demonstrated by angiographic method that those Acute Myocardial Infarction patients who experienced preinfarction angina within seven days preceding the acute event had a more rapid thrombolysis. Patency rates were higher at 35 minutes but at 90 minutes both were same.^[16]

In this study success rate was same at 90 minutes in both groups. This is because ECG monitoring was not continuous in this study. Continuous ST segment monitoring may be needed to demonstrate the early achievement of patency in preinfarction angina patients.

Smoking :

Outcome of thrombolysis is not affected by smoking. In this study there is a statistically insignificant trend towards a bad outcome. Cindy L. Gines^[17], E.J. Topol et al. reported similar patency rates in smokers and nonsmokers at 90 minutes (59.3% versus 40.9%). Smokers tend to have reduced in hospital mortality compared to nonsmokers. But this was due to the favourable baseline clinical and angiographic

variables in smokers. Smokers tended to be younger and thrombosis of less critical atherosclerotic plaque was the culprit lesion in them. Smoking increases blood hematocrit, fibrinogen levels and platelet levels contributing to the hypercoagulable state promoting coronary thrombosis.

Smokers are also found to have lesser fibrinolytic activity than nonsmokers.

Pain to streptokinase interval (time window):

This is the most powerful predictor of success rate. In this study also it is evident. Success rate was 64% in those patients thrombolysed within 4 hours from the onset of symptoms. The success rate decreased to 55%, when they were thrombolysed after 4 hrs but within 8 hours of onset of symptoms. Success rate came down to 30%, when streptokinase was administered after 8 hours but within 12 hours.

RESULTS:

The study was conducted to evaluate the success rate of thrombolysis in acute myocardial infarction and the various factors influencing its outcome. It was done by observational prospective cohort study of patients receiving streptokinase for acute myocardial infarction in intensive care unit, SRG Hospital, Jhalawar. The overall success rate of thrombolysis was 62%. Patients with inferior wall myocardial infarction had a better outcome than anterior wall myocardial infarction. Alcohol, smoking and age were factors which influence the outcome, but were not statistically significant. Early thrombolysis had a better out come when compared to other predictors. Success rate was 64% in those patients thrombolysed within 4 hrs. from the onset of symptoms. Time window was found to be the most powerful factor influencing the outcome of thrombolysis in patients with acute myocardial infarction.

A total of 60 patients were studied. Their age ranged from 31-76 years (mean 55.01). 47 of them were males and 13 females, 34 of them were hypertensives, 22 were diabetic, 32 people were smokers and 15 used to consume alcohol. 27 patients had anterior wall infarction and 33 patients had inferior wall infarction.

The outcome of thrombolysis based on the various parameters is summarized as below:

(Table 1,2 and Figure 3)

Variables	Success	Failed	Significant
Total number	37(62%)	23(38%)	
Males	29(61.7%)	18(38.29%)	Not significant
Females	8(61.8%)	5(38.4%)	
Hypertension	24(70.5%)	10(29.4%)	Not significant
Diabetes	13(59.09%)	9(40.90%)	Not significant
Smoking	19(59.3%)	9(40.9%)	Not significant
Drinking	10(66.66%)	5(33.33%)	Not significant

Figure 1 :

Variables	success	Failed	Significant
Time window			
0-4hr(14)	12(85.7%)	2(12.5%)	Significant
4-8hr(34)	22(64.7%)	12(41.1%)	X2-10.3
8-12hr(12)	3(25%)	9(75%)	P <0.05
Age group			
<60yr(41)	28(44.4%)	13(31.7%)	Not significant
>60yr(19)	9(47.3%)	10(52.6%)	
Anterior wall infarct	12(44.44%)	15(55.5%)	Significant.
Inferior wall infarct	25(75.7%)	8(24.2%)	X2-4.90 P value- <0.05
Killip grading			
1 (45)	32 (71.1%)	13(28.8%)	Significant:
2 (9)	4 (44.4%)	5(55.55%)	X2-8.6
3 (3)	1(33.33%)	2(66.6%)	P value-<0.05
4 (3)	0	3(100%)	

Figure 2 :

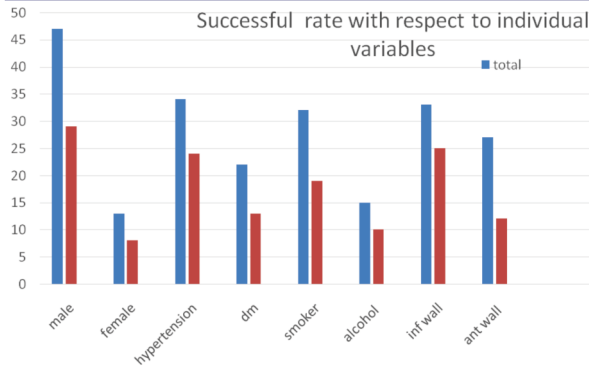


Figure 3

CONCLUSION:

In this study the overall success rate of thrombolysis was 62%. Inferior wall myocardial infarctions had a better success rate than anterior wall myocardial infarctions and it was statistically significant. Time interval between the onset of pain and time of thrombolytic administration was inversely proportional to the success rate and was highly significant. The success rate was significantly higher with a lower Killip grading and the outcome worsened as the grading increased. Smokers had a lesser success rate than non smokers, but it did not reach statistical significance. Alcohol intake was associated with a better success rate even though statistically not significant. Hypertensives didn't show much difference in the success rate. Diabetics do not differ from non diabetics with respect to the success rate of thrombolysis. There was a trend towards a worse outcome in those aged more than 60 years. But it was not statistically significant. Gender was not found to influence the success rate of thrombolysis.

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