PREDICTORS OF FAILED THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Background & objectives: Acute myocardial infarction (AMI) is becoming increasingly important problem in developing countries, and thrombolysis is the main modality of treatment here. About 25-50% of patients fail to achieve successful reperfusion and these patients have poor prognosis. Since alternative modes of reperfusion are available, it is important to identify them. This study was aimed at defining the extent of failed thrombolysis and identifying its demographic and clinical predictors

Methods: 50 cases of thrombolysed AMI patients were studied. Failed thrombolysis considered if there is < 50% resolution of ST-segment elevation after 90minutes of thrombolysis in single lead showing maximum ST elevation at presentation. The clinical predictors of the outcome were assessed.

Results: Of 50 patients studied 30(60%) achieved successful thrombolysis and 20(40%) failed. Mean time to thrombolysis from onset of symptom was 5.85 ±2.49 hrs in failed group v/s 4.55 ±2.4hrs in successful group (P<0.05).Mean age was 52.3±11.14yrs v/s 57.4±12.5yrs (P>0.05), percentage of females was 25% v/s 16.7%(P>0.05), mean time for resolution of chest pain was 3.55±1.1 hrs v/s. 1.98±0.93 hrs (P<0.001), percentage of anterior MI was 70% v/s 53% (P>0.05), inferior wall MI was 30% v/s 46% (P>0.05) in failed and successful group respectively.

Interpretation and conclusion: Late presentation is an important risk factor for failed thrombolysis in AMI. Persistence of chest pain and non-resolution of reciprocal ST depression are significantly associated with failed thrombolysis

Keywords: acute myocardial infarction; streptokinase; ST segment resolution; failed thrombolysis; time to thrombolysis; predictors of failed thrombolysis

1. Introduction

Acute myocardial infarction is one of the most common diagnoses in hospitatised patients in industrialized countries.[1] Despite the impressive strides in diagnosis and management over the past three decades, acute myocardial infarction continues to be a major health problem in industrialized world and is becoming and increasingly important problem in developing countries.[2] Because acute myocardial infarction strikes an individual during the most productive years, it can have profoundly deleterious psychological and economic ramification.[2]

The unequivocal demonstration of role of the thrombus in acute myocardial infarction quickly led to the systematic testing of thrombolytic strategies to abort myocardial infarctions.[3]

The thrombolytic therapy is the main mode of reperfusion in developing countries like India.[3] Although 60 to 70% of treated patients can be successfully reperfused, thrombolytic treatment fails in a substantial proportion. These non-responsive patients can have a significant high mortality and morbidity. Since alternative modes of coronary intervention are available, it is prudent to identify patients with failed thrombolysis so that they can be offered alternative modes of reperfusion.[4] The present study is aimed at defining the extent of failed thrombolysis and assessing its demographic and clinical predictors in our hospital. Though the study was done some years back the demographic and clinical picture are still the same, hence the results are much relevant.

2. Materials and Methods

2.1 Source of data: The present study was undertaken at Karnatak Institute of Medical Sciences (KIMS) Hospital, Hubli, South India, between April 2004 and March 2005.

50 cases of thrombolysed acute myocardial infarction (MI) were studied. Sample is drawn by simple random technique.

2.2 Sample size: Total cases - 50

Inclusion criteria:

- Patients admitted to KIMS hospital ICCU who have at least 2 out of 3 criterias for acute myocardial infarction as defined by WHO.[5]

Exclusion criteria:

- Presence of contra indications to streptokinase therapy.
- Patients presenting with evolved myocardial infarction.
- Patients dying within 90 minutes of streptokinase therapy.
- Patients presenting with left bundle branch block.

2.3 Study protocol: In patient with acute MI after considering inclusion and exclusion criteria, history and clinical examination done. Baseline ECG and other investigations (RBS, Lipid Profile, RFT, Cardiac Enzymes – if required, Hemogram) were done. Patients treated with 325mg of Aspirin orally &15 lakh units of streptokinase infusion over 1 hour. Other treatments (β-blocker, ACEI, Heparin, Analgesics) were used as indicated. Patients are assigned to successful / failed thrombolysis based on 90 min ECG after thrombolysis

Successful / failed thrombolysis is diagnosed based on ECG taken 90 min after thrombolysis. Failed thrombolysis is considered if there is less than 50% ST segment resolution in the single lead showing maximum ST elevation at baseline ECG.[6] ST elevation is measured at 80 msec from J-point.

2.4 Statistical analysis: In the present study values are expressed as mean ±1 standard deviation or as percentages. Variables are compared by student't' test. Attributes are compared by Chi square test with Yates correction. In this study strength of association is said to be significant if 'p' value ≤ 0.05.

3. Results

Based on ECG Criteria 30 patients (60%) had successful thrombolysis and 20(40%) had failed thrombolysis.

Mean age of patients was more in failed thrombolysis (57.4±12.5) than in patients with successful thrombolysis (52.3±11.14), but it was statistically not significant. Failed group had higher percentage of patient in age group > 70 yrs but it was statistically not significant.

Though the percentage of females in failed group was higher (25% v/s 16.7%) it was statistically not significant.

Risk factors for coronary heart disease: The percentage of patients with diabetes, hypertension and dyslipidemia was higher in failed thrombolysis group. The percentage of smokers and patients with BMI >23 was higher in successful group. All the above observations were statistically not significant.

Time to thrombolysis from onset of symptoms: The mean time to thrombolysis from the onset of symptoms was significantly high in patients with failed thrombolysis. Patients presenting within 3 hrs of symptoms had a strong trend towards successful thrombolysis though statistically not significant.

Heart rate and blood pressure: The distribution of patients according to those having tachycardia normal heart rate, bradycardia or systolic BP was almost similar in two groups.

Killip class at presentation: In failed group 16 patients (80%) had Killip class-I at presentation and in successful group 25 patients (83.3%). Killip class > I was seen in 4 patients (20%) in failed group, and in 5 patients (16.7%) in successful group. This was statistically not significant.

Site of Myocardial Infarction: In failed thrombolysis group 14 patients (70%) had anterior wall MI and 6 patients (30%) had non anterior MI. In successful thrombolysis group 16 patient (53.3%) had anterior wall MI and 14 patients (46.7%) had non anterior MI. This difference was statistically not significant. Size of MI: Large MI (ST elevation in ≥7 leads) was seen in 15% of patients with failed thrombolysis and 13.3 % of patient with successful thrombolysis.

Resolution of chest pain: The mean time for resolution of chest pain was higher in failed thrombolysis group ($p<0.001$). 85% patients with failed thrombolysis had chest pain for > 2hr after thrombolysis and it resolved in ≤ 2 hrs in 80% of patients with successful thrombolysis ($p<0.001$). Resolution of reciprocal ST depression: ST depression was seen in 12 and 18 patients with failed and successful thrombolysis at admission respectively. Among them 3(25%) and 15(83.3%) showed resolution of ST depression respectively which is statistically significant.

4. Discussion

In the present study we have studied the extent of failed thrombolysis in 50 patients admitted

to ICCU, KIMS hospital, Hubli, who were eligible for streptokinase therapy. We have also studied the association of failed thrombolysis with the demographic, clinical and prognostic variables.

The extent of failed thrombolysis varies from 15 to 50% in various studies. It depends on the criteria used for failed thrombolysis, drug used and inclusion and exclusion criterias used in a particular study. In present study failed thrombolysis was observed in 40% of patients using ≤50% maximum ST resolution at 90 min post thrombolysis with streptokinase as criteria.

Richardson *et al*[7] used similar criteria and drug and observed 44% failed thrombolysis. Purcell IF *et al*[8] who used 120min ECG post thrombolysis with streptokinase and Katyal VK *et al*[9] who used < 30% at 90min as criteria observed 34% failed thrombolysis. Other studies mentioned in the below table used Alteplase/Reteplase / Streptokinase and found 30-34% failed thrombolysis (table No.4)

Mean age in failed group was 57.4±12.5 yrs and 52.3±11.4 yrs in successful group. Though higher age was associated with failed thrombolysis it was statistically not significant. Similar observation was seen GISSI –2[10] and Gabriel I B *et al*[11]. But M Sezer *et al*[12], Shah A *et al*[13] and Matetzky *et al*[14] observed higher age in successful group.

Failed thrombolysis had higher percentage of females in present study though statistically not significant similar observation was made in GISSI-2[10], Gabriel IB *et al*[11] and M Sezer *et al*[12] study. Matetzky *et al*[14] found higher percentage of females in successful group.

Diabetes is one of the important risk factors for CHD and diabetics have a poor prognosis after MI which can be partly due to abnormal microvascular flow. In present study diabetics had a higher trend towards failed thrombolysis. GISSI-2[10] and Angeja BG *et al* (2002),[15] showed significant association of diabetes with failed thrombolysis.

Hypertension was seen in 20% of patients with failed and 16.7% of patients with successful thrombolysis which was not significant. Other studies also showed no significant association.

Dyslipidemia was observed in 90% and 95% of patients with successful and failed thrombolysis with no significant association. Dobrzycki S *et al* (2003),[16] showed that persistent ST segment elevation patients had higher blood LDL and total cholesterol levels than patients with early ST resolution. There was no relation with blood levels of triglycerides or HDL cholesterol .

Smoking was seen in higher percentage of patients with successful thrombolysis in present study but not significant. Similar observation was made by GISSI –2[10] and M Sezer *et al*.[12] Zahger D *et al*(1995),[17] showed that smoking was significantly associated with successful thrombolysis and lower mortality, which he attributed to incidence of acute MI in younger age and lesser atherosclerotic burden, more thrombus at the site in smokers.

Killip class at presentation: GISSI –2[10] observed that higher the Killip class, more the extent of failed thrombolysis. This indicates that patient with cardiogenic shock are better treated with PTCA if available. In present study only a minor trend is observed.

Heart rate and systolic blood pressure at presentation did not have an association with failed thrombolysis in present study.

Variations according to site infarction: Anterior wall MI was seen in 70% and 53.3% of patients with failed and successful thrombolysis respectively. Inferior wall MI was seen in 30% and 46% of patients with failed and successful thrombolysis. There was a trend towards higher occurrence of failed thrombolysis in anterior wall MI and successful thrombolysis in inferior wall MI. Gabriel IB *et al*[11] and GISSI –2[10] showed this observation in significant proportions.

Size of infarction: GISSI-2[10] showed larger infarctions have more successful thrombolysis and smaller infarction have more failed thrombolysis. Though such a difference was seen in present study it was statistically not significant**.**

Time from onset of symptoms to thrombolysis: In present study mean time to thrombolysis was significantly high in failed group (5.85±2.47 hrs) when compared to successful group (4.55±2.4 hrs). GISSI-2[10] showed significantly higher proportion of successful thrombolysis in patients presenting within 3 hours. Shah *et al*[13] and Gabriel IB *et al*[11] did not show such association.

Time for resolution of chest pain: Rapid resolution of chest pain (≤2hr) was significantly associated with successful thrombolysis. Mean duration of chest pain resolution was higher in failed group (3.55±1.1 hrs) when compared to successful group (1.98±0.93hr).Gabriel IB *et al*,[11] showed

similar results. Resolution of reciprocal ST depression was significantly associated with successful thrombolysis group (83.3%) when compared with failed thrombolysis group (25%).

Lee YY *et al*, [18] showed streptokinase had a failure rate 56.8% and history of diabetes mellitus, hypertension, anterior location of MI, longer door-to-needle time were highly predictive of thrombolysis failure using streptokinase.

Strengths of present study - simple ECG parameters are used to assess the efficacy of thrombolysis, which can be used even by non-cardiologists at a peripheral hospital. Limitations - Small number of patients studied. Angiography control not used and no interventional facilities available at our centre for failed thrombolysis.

5. Conclusion.

Long symptom to needle time is an important predictor of failed thrombolysis in acute myocardial infarction patients. Hence it is important to educate public about prompt recognition of symptoms and seeking medical help urgently. As it is also seen commonly in patients with old age, diabetes and dyslipidemia, such patients should be monitored and treated aggressively. Persistence of chest pain beyond 2 hours and non-resolution of reciprocal ST depression can serve as additional markers of failed thrombolysis. As failed thrombolysis can be associated with poor prognosis its recognition and appropriate further management is needed.

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References

1. Elliot MA, Joseph Loscalzo: ST segment elevation myocardial infarction *in* Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo. Harrison's principles of internal medicine.18h ed. New York: Mc Graw Hill; 2012: 2021-35.
2. Elliot MA, Eugene Braunwald: ST-Elevation MI *in* Libby P, Bonow RO, Zipes DP, Mann DL. BRAUNWALD`S Heart Disease. 8th ed. Philadelphia: Elsevier; 2008:1207-1300..
3. Alexander AW, Prall CM, Ryan TJ, Robert R: ST elevation myocardial infarction *in* Valentine F, Alexander RW, Robert A, Robert R, Spencer B , Ira S, *et al*. Hurst's The Heart. 11th ed. New York: Mc Graw Hill; 2004:1277-1351.
4. Mark A de Belder. Acute myocardial infarction: failed thrombolysis. Heart. 2001; 85; 104 - 112.
5. MONICA project, circulation. 1994 ; 90 ; 583-612.
6. Syed MA, Borzak S, Asfour A, Gunda M, Obeidat O, Murphy SA, *et al*. Single lead ST-segment recovery: a simple, reliable measure of successful fibrinolysis after Acute MI. Am Heart J. 2005 Feb; 147 (2) : 275-80.
7. Richardson SG, Mortan P,Murtagh JG, Scott ME, Barry BO. Relation of coronary artery patency and LV function to ECG changes after streptokinase treatment during acute MI. Am J Cardiol.1988; 61:961-5.
8. Purcell IF, Newall N. Farrer M. Change in ST segment elevation 60 minute after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes. Heart. 1997; 78 : 465-471.
9. Katyal VK, Siwach SB, Jagadish, Sharma P, Batra M. Failed thrombolysis and its impact after acute MI, J Assoc Physicians India. 2003; 51:1149-50.
10. GISSI- 2 : In hospital mortality and clinical course of 20891 patients with suspected Acute MI randomized between alteplase and streptokinase with or without heparin. Lancet.1990; 336: 71-75.
11. Gabriel IB, Arie R, Hanoch H, Hilton IM, Schemuel R, Yedahel HZ, *et al*. Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase. Heart. 1990; 64 : 241-7.
12. M Sezer, Y Nisanci, B Umman, E Yilmaz, A Olcay, F Erzengin, *et al*. New support for clarifying the relation between ST segment resolution and microvascular function. Heart. 2004;90:146-150.
13. Akbar Shah, Galen SW, Christopher BG, Christopher MO, Cynthia LG, Kathleen MT, *et al*. Prognostic implications of TIMI flow grade in infarct related artery compared with 12 lead ST segment

resolution analysis. J Am Coll Cardio. 2000; 35 : 666-72.
14. Matetzky S, Freimark D, Pierre C, Ilya N, Oren A, Babeth R, *et al*. The distinction between coronary and myocardial reperfusion after thrombolytic therapy by clinical markers of reperfusion. J Am Coll Cardiol. 1998;32:1326-30.
15. Angeja BG, Lemos J, Murphy SA, Antman EM, Cannon CP, Braunwald E, *et al*. Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. Am Heart J. 2002; 144:649-56.
16. Dobrzycki S, Kozuch M, Kamishinski K, Korecki J, Ostasz A, Podgrudna E, *et al*. High cholesterol in patients with ECG signs of no-reflow after myocardial infarction. Rocz Akad Med Bialymst. 2003; 48:118-22.
17. Zahger D, Cereck B, Cannon CP, Jordan M, Davis V, Braunwald E, *et al*. How do smokers differ from non smokers in their response to thrombolysis (The TIMI-14 trial). Am J Cardiol. 1995; 75:232-36.
18. Lee YY, Tee MH, Zurkarnai Y, Than W, Sapawi M, Suhairi I. Thrombolytic failure with streptokinase in acute myocardial infarction using electrocardiogram criteria. Singapore Med J. 2008; 49(4): 304-10.

Table-1: **Demographic and other baseline characteristics among two groups.**

	Successful thrombolysis (n = 30)		Failed thrombolysis (n = 20)		'p' value
	No.	%	No.	%	
Age>70yrs	1	3.3	3	15	NS
Females	5	16.7	5	25	NS
Diabetes mellitus	4	13.3	4	20	NS
Smoking	16	53	10	50	NS
BMI > 23	14	46.7	9	45	NS
Dyslipidemia	27	90	19	95	NS
Anterior wall MI	16	53.3	14	70	NS
Killip Class> I	5	16.7	4	20	NS

NS- not significant

Table No. 2: Time to thrombolysis from onset of symptoms among two groups.

	Successful thrombolysis (n = 30)		Failed thrombolysis (n = 20)		'p' value
	No.	%	No.	%	
Time to thrombolysis ≤3 hrs	11	33.3	2	10	p < 0.1 (NS)
Time to thrombolysis > 3 hrs	19	67.7	18	90	
Mean time to thrombolysis ±1 SD (hrs)	4.55±2.4		5.85±2.49		p <0.05(S)*

(NS) - not significant
(S)* - significant

Table No. 3: Resolution of chest pain and reciprocal ST depression among two groups.

	Successful thrombolysis(n=30)		Failed thrombolysis(n=20)		'p' value
	No.	%	No.	%	
Resolution of chest pain in ≤ 2 hrs	24	80	3	15	p < 0.001(S)*
Resolution of chest pain in > 2 hrs	6	20	17	85	
Mean time for resolution of chest pain ±1SD (hrs)	1.98±0.93		3.55±1.1		p < 0.001(S)*
ST depression resolved in	15	83.3	3	25	p < 0.01 (S)*

(S)* - significant

Table No. 4: Extent of failed thrombolysis

Study	Extent of failed thrombolysis	Drug used	Criteria of ST resolution	Time from onset of symptom - thrombolysis up to (hrs)
Richardson SG *et al*,	44%	Streptokinase	Max ST<50% at 90min	6
Gabriel IB *et al*,	34%	Alteplase	ΣST<50% at 60 min	-
GISSI-2,	33.3%	Streptokinase / Alteplase	ΣST<50% at 180 min	6
Purcell IF *et al*,	34.2%	Streptokinase	Max ST<50% at 120 min	12
Matetzky *et al*,	33.3%	Reteplase	ΣST<50% at 120 min	4
Shah A *et al*,	31.6%	Streptokinase / Alteplase	Max ST<50% at 120 min	6
M Sezer *et al*,	33.3%	-	ΣST<50% at 90 min	-
Katyal V K *et al*,	34.3%	Streptokinase	ΣST<30% at 90 min	-
Present study,	40%	Streptokinase	Max ST<50% at 90min	12

Max ST – ST elevation in the single lead showing maximum ST elevation at base line.
ΣST – Sum of ST elevation in all leads showing ST elevation.