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Research Article

Reperfusion failure: a study using electrocardiographic criteria

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ABSTRACT

Background: The incidence of ischemic heart disease and myocardial infarction is increasing in developing nations. One measure that consistently improves outcomes in patients with myocardial infarction is early reperfusion. In resource-constrained settings, reperfusion is often achieved with thrombolysis rather than percutaneous coronary intervention. Our study aimed to determine, by using electrocardiographic criteria, the failure rate of reperfusion with thrombolysis by streptokinase in patients presenting to a tertiary hospital in south India. We also aimed to find the factors associated with failure of thrombolysis in the population under study.
Methods: Patients diagnosed to have acute myocardial infarction and thrombolysed with streptokinase were taken for the study. Failure of thrombolysis was defined by electrocardiographic criteria as less than 50% resolution in ST segment elevation in the worst affected lead after thrombolysis.
Results: Reperfusion with streptokinase had a high rate of failure. Diabetes smoking longer symptom needle time and higher admission rates and blood pressure and heart rates were factors associated with failure.
Conclusion: Thrombolysis with streptokinase has a high rate of failure and certain specific factors are associated with reperfusion failure.

Keywords: Myocardial infarction, Thrombolysis, Electrocardiogram, Reperfusion failure

INTRODUCTION

The average incidence of acute Myocardial Infarction (MI) is around 208 per 100,000 person years.[1] Ischemic heart disease, previously considered a disease of the developed nations, is now affecting less developed nations too, with a large share of the global cases of ischemic heart disease being in developing countries.[2] MI carries high mortality and morbidity, and early reperfusion is the one measure that consistently improves outcomes.[1]

Early reperfusion is best accomplished by Primary Percutaneous Intervention (PPCI). However, in many regions of the world, patients present to centers that are not equipped for primary PCI.[3]

The one-year mortality rate of both PPCI and thrombolysis are similar and time delay to perfusion seems crucial to determining the outcomes. ACCF/AHA guidelines recommend that fibrinolytic therapy be instituted if the patient is being treated at a non-PCI capable hospital. In India where the majority of the population is rural, and access to PCI capable hospital is limited, early thrombolysis is a valid option for reperfusion. Thrombolysis in the setting of a developing country has some advantages namely: easily available, less expensive, easier to administer, therefore less expertise required.[4]

Thrombolysis with intravenous streptokinase has a success rate of 44%. The ECG is a low cost non-invasive method to detect the success or failure of thrombolysis, and the success of thrombolysis (achievement of TIMI 3

flow) is indicated by resolution of ST segment elevation. Certain factors are associated with failure of thrombolysis. These include longer door to needle time, high total count, diabetes, hypertension and anterior myocardial infarction.[5] Patients with factors that are associated with a failure of thrombolysis would have better outcomes with primary PCI.

Failure of thrombolysis with streptokinase and factors associated with reperfusion failure has not been studied in our population. Our study aimed to determine, by using ECG criteria, the failure rate of thrombolysis with streptokinase in acute myocardial infarction in patients presenting to our hospital on the west coast of South India. We also aimed to find factors associated with failure of thrombolysis in the population under study.

METHODS

The study was a prospective observational study conducted in a medical college hospital in Mangalore, South India. Patients with acute myocardial infarction as diagnosed by clinical features and ST elevation of at least 2 mm in 2 leads in ECG who were thrombolysed with streptokinase were included in the study. Patients who had contraindications to thrombolysis, who presented to hospital more than 12 hours after symptom onset, who had bundle branch block and those who had been previously thrombolysed with streptokinase were excluded.

A brief history and directed physical examination were done.

An ECG was recorded prior to starting streptokinase infusion. The maximum height of ST elevation in the lead that was worst affected was measured with a plastic ruler. 1.5 million Units of streptokinase were infused over 1 hour. A second ECG was recorded 90 minutes after the first. The ST elevation in the worst affected lead was measured once more and the reduction in height noted. If the reduction in the ST elevation was less than 50% then the thrombolysis was considered a failure.

The Statistical Package for Social Sciences version 13 (SPSS Inc., Chicago, IL, USA) was used for analysis of the data in our study. Mean and standard deviation was used to express the numerical data while frequency and percentages were used to record the categorical data. P <0.05 was considered as significant, chi-square test was used to compare the association of variables for categorical data and for numerical data, t-test was used.

RESULTS

This study was conducted in the city of Mangalore, a city on the west coast of South India. A total of 100 patients admitted with AMI who were thrombolysed with streptokinase were recruited of which 26 were female and 74 were male. 63 patients had failed thrombolysis with streptokinase compared to 37 patients who had a successful thrombolysis (Fisher's exact test P = 0.036) Patients with Anterior Wall MI (AWMI) had the highest rate of failure of thrombolysis (43, 68.3%) followed by Inferior Wall Myocardial Infarction (IWMI) (14, 22.2%). The mean symptom needle time in patients with failed and successful thrombolysis was 7.95 hours and 3.03 hours respectively (t test 11.95 P <0.001). 35 (55.6%) patients among the failed group had DM (OR 2.6, CI 1.1-6) (x^2 = 5.003 P = 0.025). 61% of our study population were smokers and among these 69.8% failed thrombolysis with streptokinase.

Our study showed that patients who failed reperfusion had a higher admission heart rate (102.51 beats/min) and diastolic blood pressure. The mean systolic BP in the failure group was 150 mmHg and in the successful group was at 127 mmHg.

Table 1: Results of different parameters.

		Mean ± SD	Mann Whitney Z value	P	T value
Trop T	F	0.1551 ± 0.26183	0.044	0.965	
	S	0.1578 ± 0.35991			
Platelets	F	295904.76 ± 367398.9	1.717	0.089	
	S	190867.57 ± 71680.689			
TC	F	12061.9 ± 4718.407	0.69	0.945	
	S	12178.38 ± 11961.051			
DM years	F	7.54 ± 4.061	0.031	0.975	
	S	7.58 ± 3.423			
Pack years	F	32.95 ± 16.4	1.426	0.159	
	S	26.47 ± 14.552			
FBS	F	181.88 ± 80.596		0	6.125
	S	96.97 ± 17.099			

Hb	F	13 ± 2.098		0	3.974
	S	14.55 ± 1.433			
Na	F	135.59 ± 3.191		0.008	2.711
	S	133.95 ± 2.391			
K	F	3.97 ± 0.5088		0.618	0.5
	S	3.919 ± 0.4618			
Cl	F	102.24 ± 5.018		0.073	1.811
	S	100.59 ± 2.976			
HR	F	102.51 ± 16.196		0	6.608
	S	82.7 ± 10.885			
Systolic BP	F	150.29 ± 20.484		0	6.222
	S	127.3 ± 11.983			
Diastolic BP	F	91.58 ± 10.403		0	6.22
	S	78.59 ± 9.415			
	S	3.03 ± 1.258			
Creatinine	F	1.157 ± 0.3876		0.294	1.054
	S	1.084 ± 0.2205			
HTN years	F	10 ± 4.634		0.308	1.03
	S	8.5 ± 5.721			
PACK years	F	32.95 ± 16.4		0.159	1.426
	S	26.47 ± 14.552			
Cholesterol	F	215.54 ± 67.358		0.182	1.343
	S	234.43 ± 68.859			
LDL	F	140.21 ± 39.299		0.002	3.181
	S	169.86 ± 53.458			
Age	F	58.38 ± 11.296		0.275	1.098
	S	55.97 ± 9.251			
Low HDL	43	28 ± 71	0.624	0.43	NS
	68.30%	75.70% ± 71%			
Normal LDL	20	9 ± 29			
	31.7%	24.3% ± 29.0%			
31-40 years	4	0 ± 4		0.036	SIG
	6.3%	0.0% ± 4.0%			
41-50	11	13 ± 24			
	17.50%	35.10% ± 24%			
51-60	22	17 ± 39			
	34.90%	45.90% ± 39%			
61-80	24	7 ± 31			
	38.10%	18.90% ± 31%			
Above 80	2	0 ± 2			
	3.20%	0% ± 2%			
High LDL	39	28 ± 67	1.999	0.157	NS
	61.90%	75.70% ± 67%			
Normal LDL	24	9 ± 33			
	38.1%	24.3% ± 33.0%			
High TGL	39	18 ± 57	1.671	0.196	NS
	61.90%	48.60% ± 57%			
Normal TGL	24	19 ± 43			
	38.10%	51.45% ± 43%			
High cholesterol	38	26 ± 64	1.002	0.317	NS
	60.30%	70.30% ± 64%			
Normal cholesterol	25	11 ± 36			
	39.7%	29.7% ± 36.0%			
Non smokers	19	20 ± 39		0.01	SIG
	30.20%	54.10% ± 39%			

Heavy smokers	32	8 ± 40			
	50.80%	21.60% ± 40%			
Moderate smokers	10	9 ± 19			
	15.90%	24.30% ± 19%			
Occasional smokers	2	0 ± 2			
	3.20%	0% ± 2%			
	66.70%	75.70% ± 70%			
DM					
N	28	25 ± 53	5.003	0.025	SIG
	44.4%	67.6% ± 53.0%			
Y	35	12 ± 47			
	55.60%	32.40% ± 47%			
HTN					
N	29	19 ± 48	0.264	0.607	
	46.0%	51.4% ± 48.0%			
Y	34	18 ± 52			
	54.0%	48.6% ± 52.0%			
High creatinine	19	19 ± 38	6.131	0.047	SIG
	30.20%	51.40% ± 38%			
Normal creatinine	32	16 ± 48			
	50.80%	43.20% ± 48%			
	19%	5.40% ± 14%			
Anterior infarct	43	7.00% ± 50		0	HS
	68.30%	18.90% ± 50%			
Inferior infarct	14	8 ± 22			
	22.20%	21.60% ± 22%			
Lateral infarct	4	17 ± 21			
	6.30%	45.90% ± 21%			
Antero septal infarct	2	5 ± 7			
	3.20%	13.50% ± 7%			
Normal ESR	39	34 ± 73	10.635	0.001	HS
	61.90%	91.90% ± 73%			
High ESR	24	3 ± 27			
	38.10%	8.10% ± 27%			

DISCUSSION

The findings from CAPTIM and Prague 2 conclude that a PPCI is the best reperfusion strategy for AMI if done within 1 hour. Between 1 and 3 hours, thrombolysis is effective and beyond three hours, thrombolysis is less effective and the patient should be transferred to a center for PPCI. However, in developing countries, not all patients present to a center that is equipped for PCI. In such cases early thrombolysis confers a survival benefit.[6]

In developed nations, reperfusion strategies include PCI and thrombolysis with tissue plasminogen activator (t-PA). The GUSTO trial did not find any significant difference between the 30 day mortality in patients thrombolysed with t-PA and streptokinase.[7] However at the end of the first year of follow up, mortality rates were significantly lower with t-PA than with streptokinase.[8] In spite of this, it must be taken in to account that t-PA costs ten times as much as streptokinase and health care in developing countries like India is paid for by the individual, as health insurance systems are not completely in place yet. Therefore, streptokinase continues to be a viable treatment option in developing countries to achieve reperfusion in patients admitted with acute MI.[9]

Coronary artery disease in India has a prevalence of 64.37 per 1000 people and is anticipated to affect 65 million Indians by the year 2015. Patients in India admitted with an ACS have a higher rate of STEMI than those in developed nations.[10]

The problems regarding care of acute myocardial infarction in India are, firstly that a well-equipped trained Emergency Medical Service (EMS) to administer pre hospital thrombolysis is not yet in place, and secondly health insurance is not universal, and patients often pay out of pocket for medical care. This means that in a country that has the lowest per capita income among the

G 20 nations; cost of therapy becomes a major consideration. Coronary vascular disease is no longer a disease of the wealthy and in caring for the poor who present with myocardial infarction, often to a centre that is not PCI capable, the financially more appropriate thrombolytic agent streptokinase is often used.

Our study aimed at quantifying the failure rate of thrombolysis with streptokinase in acute myocardial infarction and finding patient and logistic factors associated with failure. Failure of thrombolysis was defined as less than TIMI 3 flow after thrombolysis. We used ECG criteria as a bedside non-invasive test to determine success/failure of thrombolysis. Sutton et al defined ECG criteria for failure of thrombolysis as less than 50% resolution of ST segment elevation in the most affected lead and absence of idioventricular rhythm.[11]

Our study demonstrated a 63% failure rate of thrombolysis with streptokinase. Higher failure rates were seen in diabetics, patients with anterior infarct, and with a longer symptom to needle time. A highly significant correlation was found between failed thrombolysis and high admission blood pressure, tachycardia, and high serum sodium.

The higher failure rate in our study - 63% vs. 54% in GUSTO 1 trial is perhaps due to the much higher symptom needle time. The catchment area of the study centre is the surrounding villages and small towns. The area is mountainous and rapid travel is difficult. Therefore significantly longer time is taken to reach hospital from the time of symptom onset. The effect of the location of the occluded artery on thrombolysis varies. In our study, patients with anterolateral MI had the highest failure rates, similar to previous studies, including the INJECT trial.[12] However in the GUSTO 1 study, patients with occlusion of the right and left circumflex arteries had worse outcomes than those with occlusion of the Left Anterior Descending artery (LAD).[7] The influence of the occluded artery on the outcome of thrombolysis is influenced by the thrombus burden, plaque burden and also the development of collaterals.

Previous studies show that the single factor with greatest effect on the success of reperfusion after an infarction is the timeliness of reperfusion. Myocardial necrosis is a process that increases with the elapse of time, with the muscle fibre passing through the stages of dysfunction, stunning and finally death.[13] This was corroborated in our study in which the mean Symptom Needle (S/N) time in the successful group was 3.03 hours as opposed to 7.95 hours in the group, which failed reperfusion. Even in the developed world, the time to admission and the time to treatment in patients admitted with MI is still prolonged, and resources must be allocated to improve these times.[14]

10 to 25% of patients admitted with MI have diabetes mellitus. In our study the figure was 47%, which is unsurprising, as India has a high prevalence of diabetes mellitus. Our study demonstrated a poor thrombolytic outcome in patients with diabetes, with 55.6% of those who failed thrombolysis being diabetics. The increased failure rates in diabetics are due to decreased myocardial sensation, leading to increased symptom needle time. Admission blood glucose level after AMI is an independent predictor of long-term mortality in patients, even in patients without diabetes, and among patients who are not known diabetics, admission glucose levels of 200 mg/dL or more after MI have mortality rates comparable to those of established diabetics.[15]

Admission glucose was found to be a better predictor of long-term outcome than HbA1c.[16]

In our study there was no difference between the S/N times in diabetics and non-diabetics unlike in previous published reports. This may be due to the general tendency to an increased S/N time in most of our patients.

In our study hypertension and higher admission blood pressure showed a correlation with reperfusion failure. Other studies also show that hypertensives have a higher rate of stroke and sudden cardiac death.[17] This may be related to factors such as left ventricular hypertrophy and endothelial damage.[18] This might indicate a greater need to normalize blood pressure before starting thrombolytic therapy or switching to alternate means of therapy if the pressure remains high. In our study, tachycardia at admission was associated with a higher rate of reperfusion failure. This has been demonstrated in other studies as well, and is perhaps due to the fact that tachycardia increases oxygen demand and cardiac work.[19] This effect of the heart rate on outcome is further worsened by diabetes mellitus.[20]

Our study showed that the rate of reperfusion failure increased with advancing age. In addition, elderly patients who are admitted with MI have higher rate of stroke, cardiogenic shock, bleeding and reinfarction.

Many of the elderly who are admitted with acute MI have contraindications to thrombolysis. Therefore, thrombolysis in the elderly is less effective and safe than in the young.

We found that smokers, especially heavy smokers, had a higher rate of failure of reperfusion. However, previous studies show no difference in mortality between smokers and non-smokers, and one retrospective study shows that smokers admitted with acute MI have better outcomes than non-smokers.[21] This phenomenon, where smokers admitted to hospital with myocardial infarction have a better outcome is known as the smokers' paradox. However, this is perhaps because smokers present at a younger age, and have a lower incidence of diabetes and hypertension, and the early presentation and the absence of comorbidities are perhaps responsible for this observation.[22]

Limitations of the study

This was a purely observational study on patients who presented to hospital with acute MI, and who refused the option of PPCI. It excluded patients who could afford PPCI, and those who were thrombolysed with more expensive tenecteplase, which is superior to streptokinase. Since the aim of the study was to find the rate of failure of thrombolysis, as determined by ECG criteria, with streptokinase and factors associated with failure, the patients were not followed up for study purpose after thrombolysis. Some of the patients underwent rescue angioplasty; however these details were not collected or analyzed.

CONCLUSION

In many developing countries, including India, PCI is not as easily accessible as it is in the developed world, and thrombolysis is a financially more affordable alternative, which is often used. However, in acute myocardial infarction, thrombolysis with streptokinase had a high rate of failure of reperfusion, and factors associated with failure were increased symptom needle time, diabetes, increased Admission blood pressure, smoking, and in the elderly. Therefore in spite of the increased cost, these are patients who would benefit from referral for primary percutaneous intervention.

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Ethical approval: The study was approved by the institutional ethics committee

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