A Cross-Sectional Study of Comparative Coronary Angiographic Profile of Successful and Failed Thrombolysis with Tenecteplase Conducted at Osmania General Hospital, Hyderabad

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ABSTRACT

BACKGROUND

Acute Myocardial Infarction (AMI) can lead to death, and thrombolytic therapy (TLT) is a common treatment protocol. However, thrombolysis is not always successful, and there are numerous contributing factors. We wanted to compare and contrast the coronary angiographic profile of patients with successful and failed thrombolysis with tenecteplase.

METHODS

Cases of AMI receiving tenecteplase were categorized as successful and failed thrombolysis groups. Fifty patients in each group were compared for various characteristics such as age, sex, risk factors, time to thrombolysis, LV function, number of coronary vessels involved, angiographic lesion characteristics, thrombolysis in myocardial infarction (TIMI) flow, and to look for features that may predispose to thrombolysis failure. To determine the association between variables, chi-square test and logistic regression were used.

RESULTS

The mean age in the successful & failed thrombolysis group was 50.72 years and 53.48 years. Gender, diabetes, hypertension, smoking, alcohol, type of MI were not statistically significant for failed thrombolysis. All patients with window period < 3 hrs had successful thrombolysis and most patients with window period > 6 hrs had failed thrombolysis (87.2 %). ($P < 0.001$). Most patients (75.9 %) with Type A lesions had successful thrombolysis and patients with Type B & C lesions (88.1 %) had failed thrombolysis. ($P < 0.001$).

CONCLUSIONS

In patients with longer window periods, failed thrombolysis was more common and was associated with complex coronary lesion morphology. This study reemphasizes the value of early thrombolysis for effective reperfusion and clinical outcome improvement.

KEYWORDS

Failed Thrombolysis, Tenecteplase, Angiographic Profile

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BACKGROUND

Acute myocardial infarction is one of the common causes of death. Worldwide, 30 - 70 % of patients with myocardial infarction receive thrombolysis as the initial treatment. Failure of Thrombolysis in the Indian scenario was seen in 30 - 40 % of patients.[1] The prevalence of Coronary artery disease (CAD) has progressively increased in India, i.e., two times higher (10 %) in urban than in rural India.[2,3] Thrombolysis remains the most commonly used treatment in acute myocardial infarction. The patency rates of recently available thrombolytics were about 85 %.[4] In the past, the major treatment protocol was thrombolysis with fibrin non-specific agents; subsequently, with more fibrin-specific agents, the infarct artery's patency rate has been better compared to the non-specific fibrin agents. The patency rate and T.I.M.I flow after thrombolysis is based on the agent used, either a fibrin specific or non-specific agent or several factors predicted the response to thrombolytics.[5]

The current treatment strategy for acute MI is the primary percutaneous intervention. The patency rate and grade of T.I.M.I flow is better with primary percutaneous intervention when compared to thrombolytics. A patent artery has a better prognosis than patients with an occluded vessel.[6-9] Fibrinolysis has been shown to improve both short term and long term survival.[10,11] Similarly, every 30 - minute delay in the symptom onset to percutaneous intervention increases the relative risk of 1 yr. mortality by 8 %. The ultimate goal of reperfusion in acute MI is tissue perfusion, whether due to primary coronary intervention or fibrinolytic therapy. Evidence exists on infarct-related arteries as a key determinant to knowing that reperfusion outcome is accomplished by fibrinolytic or PCI.[12-14] This study analyses various demographic factors associated with failed thrombolysis by coronary angiographic profile. In India, Thrombolysis remains the main treatment as compared to Percutaneous transluminal coronary angioplasty (PTCA), and the prognosis is poor. So through this study we intend to compare and contrast the coronary angiographic profile of patients with successful and failed thrombolysis with Tenecteplase.

METHODS

It was a single-centre, prospective observational study. The study involved 100 patients from January 2018 to November 2019. Patients diagnosed with acute MI who were given a single fixed bolus of Tenecteplase were considered. These 100 patients were grouped into thrombolysis-successful and thrombolysis-failed groups.

Patients hospitalized with acute myocardial infarction who underwent Tenecteplase thrombolysis and were hemodynamically stable with normal renal parameters were subjected to coronary angiography. The study excluded patients with contraindication for thrombolysis, evolved myocardial infarction, history of old myocardial infarction, left bundle branch block associated with myocardial infarction, chronic kidney disease, and patients thrombolysed with agents other than Tenecteplase.

Patients with acute myocardial infarction diagnosed based on the electrocardiographic criteria and thrombolysed with a single weight-based bolus dose of Tenecteplase were studied. Patients were classified as successful thrombolysis if there was more than 50 % S.T. segment resolution 90 minutes after thrombolysis in the lead with maximum S.T. elevation. Patients were classified as failed thrombolysis if the S.T. segment failed to show greater than 50 % resolution in the lead with the maximum S.T. elevation taken 90 minutes after the onset of the thrombolysis with persistent chest pain.

All patients underwent echocardiography with a PHILIPS IE33 machine. Left ventricle (LV) function was assessed by the modified Simpsons method. Patients were classified as having good LV function if the Ejection Fraction was > 50 %, and patients with LV dysfunction were sub-classified as mild, moderate, and severe if Ejection Fraction was > 40 %, 40 % to 30 %, and < 30 % respectively. The coronary angiogram was done within 48 to 72 hrs of hospital admission with Siemens Axiom Artis. The majority of patients underwent radial coronary angiography. Optimal angiographic views were taken. Patients were diagnosed with significant CAD if the stenosis was more than 50 % compared to normal vessel luminal diameter. Patients in the study population were divided into a single vessel, double vessel, and triple vessel diseases depending on the number of coronary arteries involved.

The institutional ethics committee approved this study (IEC NO: 17600001008D) and written informed consent was taken from all participants.

Statistical Analysis

Data entry was done using Microsoft Excel and analysis using R Studio software. Continuous variables were represented as mean and standard deviation. Categorical variables were represented as frequencies and percentages. The difference in the outcome variables between the groups was considered statistically significant if $P \leq 0.05$. To determine the association between variables, Fischer exact test, chi-square test, t-test, and logistic regression were used. The area under the curve (A.U.C.) of the receiver operating characteristic curve (R.O.C.) has been obtained for quantifying the model predictability. The prediction probabilities used for calculating the R.O.C. curves were done using 5-fold cross-validation.

RESULTS

Myocardial infarction was more common in the age group between 40 and 60 years. The mean age in the successful & failed thrombolysis group was 50.72 years and 53.48 years, respectively. chi-square test was used for comparing the age distributions of both groups. There was no significant difference between the two groups with a P - value of 0.3, which was not statistically significant. (Fig. 1)

Forty-two male and eight female patients enrolled in the successful thrombolysis group, while 33 male and 17 female participants enrolled in the failed thrombolysis group. Gender was not statistically significant between the two groups. The odds ratio and corresponding 95 % confidence interval was 0.373 (0.123, 1.049).

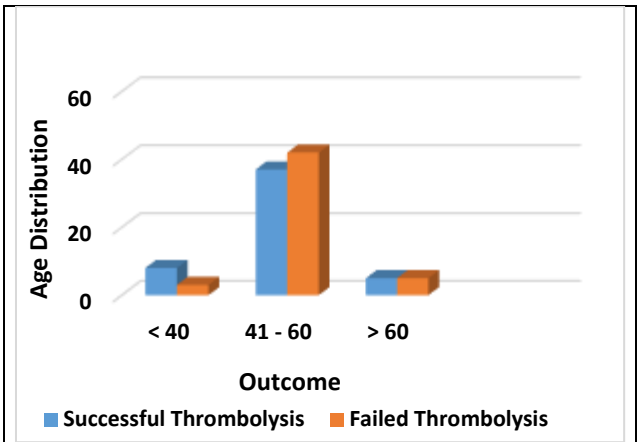

Figure 1. Distributions of Age in Groups

Variable		Groups: Successful Thrombolysis	Groups: Failed Thrombolysis	P - value (Chi-Square Test)
AWMI	N	19 (54.3 %)	16 (45.7 %)	0.675
	Y	31 (47.7 %)	34 (52.3 %)	
IWMI	N	31 (47.7 %)	34 (52.3 %)	0.675
	Y	19 (54.3 %)	16 (45.7 %)	
HTN	N	19 (54.3 %)	16 (45.7 %)	0.675
	Y	31(47.7 %)	34 (52.3 %)	
DM	N	29 (54.7 %)	24 (45.3 %)	0.423
	Y	21(44.7 %)	26 (55.3 %)	
Smoking	N	21 (48.8 %)	22 (51.2 %)	1
	Y	29 (50.9 %)	28 (49.1 %)	
Alcohol	N	29 (50.0 %)	29 (50.0 %)	1
	Y	21 (50.0 %)	21 (50.0 %)	

Table 1. Comparison between Different Variables

*AWMI: anterior wall myocardial infarction † IWMI: Inferior wall myocardial infarction; ‡HTN: hypertension § DM: diabetes mellitus

Variable		Group: Successful Thrombolysis	Group: Failed Thrombolysis	P - value (chi-square test)	P - value logistic regression chi-square
Window Period (categorical)	< 3 Hours	12 (100 %)	0 (0 %)	< 0.001	1.158 E -13
	3 - 6 Hours	32 (78.0 %)	9 (22.0 %)		
	> = 6 Hours	6 (12.8 %)	41 (87.2 %)		
Window Period (Intercept)	**Estimate (Log ODDs)**	**Std. Error**	**z value**	**Pr (> | z |)**	**Estimate (Odds)**
	7.5898	1.5128	5.017	5.25e - 07 ***	
	- 1.1763	0.2247	- 5.235	1.65e-07 ***	0.3

Table 2. Comparison of Window Period and Thrombolytic Outcomes

Signif. Codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1; AUC: 0.8888

Sixty-five patients had an anterior wall myocardial infarction (A.W.M.I.). Among patients with A.W.M.I., 31 patients (47.7 %) had successful thrombolysis, and 34 patients (52.3 %) had failed thrombolysis with a P - value of 0.68, which was statistically not significant. Hence there was no prediction of A.W.M.I. in favour of either successful or failed thrombolysis. The odds ratio and corresponding 95 % CI was 1.3 (0.528, 3.23).

Thirty-five patients had an Inferior wall myocardial infarction (I.W.M.I.). Among them, 19 patients (54.3 %) had successful thrombolysis, and 16 patients (45.7 %) had failed thrombolysis with a P - value of 0.68, which was statistically not significant. Hence there was no predilection of I.W.M.I. in favour of either successful or failed thrombolysis. The odds ratio and corresponding 95 % CI was 0.77 (0.31, 1.9). Sixty-five patients had hypertension, and among them, 31 patients (47.7 %) had successful thrombolysis, and 34 patients (52.3 %) had failed thrombolysis. The difference between the two groups was not statistically significant, with a P - value of 0.68. Among 47 Diabetic patients, 21 patients (44.7 %) had successful thrombolysis, and 26 patients (55.3 %) had failed thrombolysis. The difference between the two groups was not statistically significant, with a P-value of 0.423. Among 57 smokers, 29 (50.9 %) had successful thrombolysis, and 28 (49.1 %) had failed thrombolysis. This difference between the two groups was not statistically significant, with a P - value of 1.

All 12 patients (100 %) had successful thrombolysis with a window period of fewer than 3 hours. Among 41 Patients with window period between 3 - 6 hrs., 32 (78.04 %) had successful thrombolysis, and nine (21.9 %) had failed thrombolysis. Among 47 Patients with window period > 6 hrs., six (12.7 %) had successful thrombolysis, and 41 (87.2 %) had failed thrombolysis. The patients with a shorter window period had a very high chance of successful thrombolysis with a P - value of < 0.001, which was statistically significant.

Sixteen patients (32 %) in the successful thrombolysis group had good LV function, and only four patients (8 %) in the failed thrombolysis group had good LV function. Only four patients (8 %) in the successful thrombolysis group had moderate LV dysfunction, whereas nearly 20 patients (40 %) in failed thrombolysis group had moderate LV dysfunction. None of the patients in successful thrombolysis had severe LV dysfunction, and one patient in failed thrombolysis group had severe LV dysfunction. 30 patients (60 %) in successful thrombolysis had mild LV dysfunction, and 25 patients (50 %) in failed thrombolysis had mild LV dysfunction. A higher degree of LV dysfunction was more common in patients of failed thrombolysis than in patients with successful thrombolysis with a P - value of < 0.01 which was statistically significant.

The statistical data was interpreted as patients with multivessel disease [Triple vessel disease (TVD) and Double vessel disease (DVD)] and as those with single-vessel disease. A total of 50 patients had single-vessel disease, of which 58 % were in the successful thrombolysis group and 42 % in the failed thrombolysis group. Fifty patients had multivessel disease, of which 42 % were in the successful thrombolysis group and 58 % in the failed thrombolysis group**,** which was statistically not significant (P - 0.1615).

Fifty-four patients had Type A lesions, and among them, 41 patients (75.9 %) had successful thrombolysis, and 13 patients (24 %) had failed thrombolysis, which was statistically significant (P < 0.01). Total patients with Type B & C lesions together were Forty-two and among them, 37 patients (88.1 %) had failed thrombolysis, and Five patients

(11.9 %) had successful thrombolysis, which was statistically significant (P < 0.001)

Forty-nine patients had T.I.M.I flow ranging from 0, 1 & 2 and among them, forty-four patients (89.8 %) had failed thrombolysis and five (10.2 %) patients had successful thrombolysis. Fifty-one patients had T.I.M.I 2 flow and among them, 40 patients (88.9 %) were in failed thrombolysis group, and five patients (11.1 %) were in the successful thrombolysis group with a statistically significant P value of < 0.01. Fifty-one patients had T.I.M.I 3 flow and among them, 45 patients (88.2 %) had successful thrombolysis, and six patients (11.8 %) had failed thrombolysis with a statistically significant P value of < 0.01.

Window period, lesion type had significant P - values and it could be concluded that using Window period, and lesion type, thrombolysis' success with Tenecteplase could be predicted with high accuracy.

Variable		Group		Chi-square (P Value)
		Successful Thrombolysis	Failed Thrombolysis	
No of Vessels Involved	SVD	29 (58 %)	21 (42 %)	0.1615
	DVD & TVD	21 (42 %)	29 (58 %)	
Lesion Type	A	41 (75.9 %)	13 (24.1 %)	< 0.001
	B&C	5 (11.9 %)	37 (88.1 %)	
TIMI Flow	0,1 &2	5 (10.2 %)	44 (89.8 %)	< 0.001
	3	45 (88.2 %)	6 (11.8 %)	

Table 3. Coronary Angiographic Profile with Thrombolysis

*SVD: single vessel disease †DVD: double vessel disease ‡TVD: triple vessel disease

DISCUSSION

Tenecteplase is a bioengineered, third-generation thrombolytic with advantages that can overcome the previous generation of thrombolytic drugs' limitations. It scores well in terms of efficacy, safety, and convenience of use. This drug's various advantages include better fibrin specificity, fibrin selectivity, faster onset of action, and longer half-life. Both reteplase and alteplase fall short of these four criteria. Another key difference is Tenecteplase has a high resistance to plasminogen activator inhibitor-1 (PAI - 1) than alteplase and reteplase. It has comparable efficacy and a lower rate of major bleeding, as documented in the ASSENT-2 study.[15]

Failure of reperfusion may be due to diffuse degree of critical narrowing or microvascular no-reflow. Multiple factors for failed thrombolysis have been hypothesized.[2]

A) Haematological

- Blood levels of fibrinogen and lipoproteins
- Thrombin / antithrombin III complexes

B) Mechanical

- Pressure in the arteries proximal to the level of occluding thrombus
- Myocardial wall tension
- Thrombus burden
- Lesion complexity
- Characteristics of the plaque.
- Residual stenosis after initial reperfusion
- Sub intimal haemorrhage.

C) Unspecified Genetic Differences

Though Tenecteplase was used as the thrombolytic agent in our study, this study did not assess the drug's efficacy. Instead, 50 patients each of successful and failed Thrombolysis with Tenecteplase were taken, and various factors were compared and analysed between the two groups to look for factors that may have a predilection for having successful or failed thrombolysis.

In the Assent-2 trial, thrombolytic treatment with Tenecteplase showed that the patients who presented to the hospital less than 6 hrs of the onset of chest pain had a better prognosis than patients who presented late.[3] In S.S Iyengar et al. study "Pharmacologic Reperfusion Therapy with Indigenous Tenecteplase in 15,222 patients with S.T. Elevation Myocardial Infarction - The Indian Registry"[4] higher success rate (96.54 %) of thrombolysis was seen in patients treated within 3 hours than patients presenting more than 6 hours (85.38 %). In our study, time to thrombolysis was the most important factor determining the success or failure of thrombolysis. Twelve patients in our study presented within 3 hrs of chest pain, and all the 12 patients (100 %) had successful thrombolysis. Forty-seven patients presented after 6 hrs, and 41 patients (87.2 %) of them had failed thrombolysis.

GISSI-2 trial, which used Streptokinase / Alteplase, showed a significant association of diabetes with failed thrombolysis. In a study done by Sudhindra Rao et al. 20 percent of the diabetic population had failed thrombolysis compared to the patients with successful thrombolysis in which only 13 % had diabetes mellitus, which was not statistically significant.[5] In our study, though diabetic patients had more failed thrombolysis, it was not statistically significant. S.S Iyengar et al. study also showed similar observation wherein diabetes was not associated with any predilection for having failed thrombolysis, and diabetes was present in 95.14 % of patients with successful thrombolysis.

Sudhindra Rao et al. showed that 20 % of patients in the failed thrombolysis group had hypertension and 16 % in the successful group, which was not statistically significant. In our study, 47.7 % of hypertensives had successful thrombolysis, and 52.3 % had failed thrombolysis. Though the hypertensives had more failed thrombolysis, the difference was not statistically significant. S.S Iyengar et al. study also showed a similar observation wherein hypertension was not associated with any predilection for having failed thrombolysis, and hypertension was present in 95.83 % of patients with successful thrombolysis. The GUSTO 1 trial's angiographic data, which used streptokinase, showed a higher T.I.M.I. flow in the patients who were smokers compared to that of the non-smokers.[16] The possible mechanism is increased thrombus in smokers, while the non-smokers have more possibility of atherosclerotic disease. In our study, 50.9 % of smokers had successful thrombolysis, and 49.1 % had failed thrombolysis with a P - value of 0.84, which was not significant.

S.S Iyengar et al. showed that anterior wall myocardial infarction was associated with less successful thrombolysis. In our study, patients with anterior wall myocardial infarction had more failed thrombolysis than inferior wall myocardial infarction (52.3 % v/s 45.7 %). It was not statistically significant.

Milena Henzlova et al. showed that patients with acute myocardial infarction treated with thrombolysis early after the onset of symptoms appear to have better LV function and the ejection fraction remained stable even at one-year of follow-up. In our study, the presence of a higher degree of LV dysfunction was more common in patients of failed thrombolysis group than in patients with successful thrombolysis with a P - value of < 0.01, which was statistically significant. T.I.M.I flow of grade 3 is important for successful thrombolysis. Sutton et al. their study showed that patients had mortality benefits only if they achieved a T.I.M.I 3 flow. Gusto's trial suggested that the successful thrombolysis of the patients was based on the T.I.M.I 3 flow after thrombolysis. Jeffrey et al. in the TEAM -3 studies showed that patients with T.I.M.I 3 flow had more ejection fraction and lesser death rate. In our study, there was a strong predilection for patients with successful thrombolysis group to have T.I.M.I 3 flow and patients with failed thrombolysis group to have less than T.I.M.I 3 flow in the infarct-related artery with a significant P value of < 0.01.

In our study, gender variable comparison between the successful thrombolysis and the failed thrombolysis was not statistically significant with a P - value of (0.07). A similar observation was seen in the S.S Iyengar et al. study. There was no significant difference in the age-wise variable of presentation between the failed thrombolysis and the successful thrombolysis group with the P value of (0.27), which is not statistically significant. Our study did not comprise of any patients older than 70 years. In the S.S Iyengar et al. study, the success rate was significantly lower in patients over 70.

In our study, Single vessel or Multivessel disease's presence did not show any predilection towards successful or failed thrombolysis. In contrast, based on the lesion characteristics of the infarct-related artery, it was observed that Type A lesions showed strong predilection towards successful thrombolysis, and Type B and Type C lesions showed strong predilection towards failed thrombolysis.

CONCLUSIONS

In cases of failed thrombolysis, patients most commonly presented to the hospital after 6 hours of chest pain onset. Even though diabetes and high blood pressure increase the risk of thrombolysis failure, it was not statistically significant. Type B and Type C lesions in the infarct-related artery were more common in patients with failed thrombolysis. A higher degree of LV dysfunction was more common in patients with failed thrombolysis. Less than T.I.M.I. 3 flow was seen in patients with failed thrombolysis. With a higher number of participants, a larger study would provide better insight into the mechanisms of failed thrombolysis and the prognosis.

Limitations

1. Single centre nonrandomised study
2. Small sample size.
3. S.T. segment changes can be dynamic, and therefore errors can occur in the interpretation.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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