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Original Research Paper

Cardiology

A COMPARATIVE ANALYSIS OF EFFICACY OF THROMBOLYTICS IN ACUTE ST ELEVATION MI AND ITS VARIATION WITH CIRCADIAN RHYTHM

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ABSTRACT

Background: Fibrinolytics are the commonest modality of treatment in ST elevation Mi in India. However there is paucity of data regarding successful ST resolution and diurnal its variation

Material and Methods: 150 cases of acute ST elevation MI were administered Thrombolytics(Streptokinase-104 and Tenecteplase-46) in a coronary care unit at a tertiary hospital in Delhi. ST resolution on ECG was assessed at 30,60,90,120 and 180 minutes post Infusion. Percentages of patients going ST resolution was compared by Kaplan Meir Survival plot. Complications and Adverse Effects of Thrombolytics was noted.

Results: Tenecteplase had a significantly faster rate of successful ST resolution than Streptokinase . Hazard ratio 1.7(95% C.I. 1.093-2.66, p=0.02). Diurnal variation was associated with ST resolution(r=-0.17,p<0.001) and onset of symptoms(r=-0.17,p=0.03) which was worse in mornings. Safety Profile of both drugs was similar.

Conclusion: Our study shows that tenecteplase is associated with faster complete ST resolution. Streptokinase has a good safety profile but higher allergic reactions. There is a circadian variation in onset and severity of Myocardial infarction which is attenuated in Diabetic subgroup.

KEYWORDS : THROMBOLYTICS, ST RESOLUTION,ST ELEVATION MI

Introduction

Myocardial infarction is one of the most fatal emergencies in Lower and Middle-Income Countries.[1] In absence of invasive modalities and expertise fibrinolytics still remain primary modality for treating acute onset ST-elevation Myocardial infarction in the developing world.[2,3]

While there have been comparative randomized RCTs between many fibrinolytics[4–7], head to head trials comparing Tenecteplase to streptokinase are lacking. In India due to wide variation in practice, both continue to be used at various centers.[8] So there is a relative paucity of data comparing the efficacy and safety profile of both agents.

Some studies have postulated a circadian variation in onset and severity of myocardial infarction due to autonomic and hemostatic variation in physiology with conflicting results.[9–11] This variation can have a profound impact on "fibrinolytic first" practical management of STEMI at various centers in resource-constrained developing countries, as the more severe acute coronary events will be less likely to respond to fibrinolytics.

Early ST resolution is a cheap but less commonly employed marker of short, intermediate and long-term prognosis[12] in Myocardial infarction in absence of invasive measures like TIMI flow and Regional wall motion abnormalities.

Our aim in this study was to assess the comparative efficacy of streptokinase and tenecteplase as measured by ST resolution and complications. We also aimed to evaluate the safety profile of thrombolytics and circadian variation if any in onset and response to fibrinolytics.

Materials and Methods

Patients admitted to the coronary care unit of Hindu Rao Hospital with the diagnosis of ST elevation MI were included in this prospective cohort study. 170 patients were screened- * Patients between 20-80 years of age were included. * Exclusion criteria: NSTEMI, MI associated with Bundle branch block, contraindications to the therapy (history of intracerebral bleed, recent stroke, major surgery, head trauma or accident) or symptom to the presentation time of greater than 12 hours.

Baseline Data were collected on patient proforma with relevant parameters.

Administration

Streptokinase infusion was administered at the standard dose of 1.5 million units over 60 minutes. ECG was recorded prior to infusion, and at 60,90,120,180 minutes after start respectively to assess ST resolution. Tenecteplase was dosed according to weight (30-50 mg) as IV Bolus concurrently with an intravenous bolus of 30 mg enoxaparin followed by 1 mg/kg subcutaneously BID with other antiplatelet, statins and antianginal medication as per patient need.

Outcome

Measuring ST resolution : Maximum (vertical) ST elevation was measured in worst infarct lead using a standard ruler, at ST segment(80 ms from J point) using a standard caliper in mm. The vertical height of ST-segment elevation in the lead with the maximum ST-segment elevation (worst infarct lead), before and after streptokinase was measured using a standard ruler in mm. The ST segment was measured 80 ms from J point, which corresponded to the peak of ST elevation ST resolution at 180 minutes after start of infusion/Bolus was classified into following grades-

- 70%-100% - Complete resolution
- 30%-70% - Partial resolution
- <30% - No resolution.

Statistical Plan

Baseline characteristics between two fibrinolytics groups were compared with the use of the two-sample t-test for numeric variable and chi-square test/rank correlation was evaluated between categorical variables. Kaplan Meir curve was drawn to compare Failure of complete resolution at 30,60,90,120,180 minutes between two fibrinolytic regimes.

Tests of Proportion was done to compare adverse effects and complication between two fibrinolytic strategies. Statistical data are expressed as Median (range) or Mean (± Standard deviation) for

continuous variables or as rates (percentage) for categorical variables. The data were analyzed using the R software version 3.4.3

Results

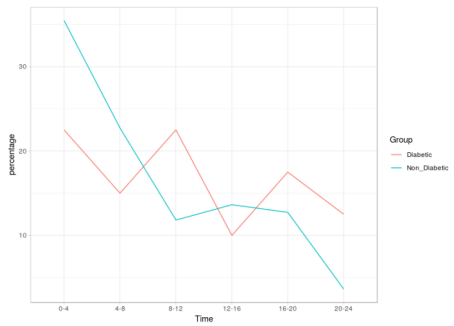
The study screened 170 patients. 150 patients(104-Streptokinase and 46 Tenecteplase) had complete records and were included in the final analysis. The Demographic table is presented in **Table 1.** There was no significant difference between baseline variables-Age, sex, Diabetes, Hypertensives, smokers and location of infarct we could potentially affect the prognosis of the patient and efficacy of thrombolytics indicating appropriate randomization.

Table 1: Baseline Demographic Table

VARIABLE		STREPTOKINASE	TENECTEPLASE	P VALUE
n		104	46	
age (mean (sd))		49.54 (15.70)	50.41 (15.97)	0.755
sex (%)	female	26 (25.0)	11 (23.9)	1
	male	78 (75.0)	35 (76.1)	
Diabetic (%)	Diabetic	31 (29.8)	9 (19.6)	0.268
	Non_Diabetic	73 (70.2)	37 (80.4)	
Hypertensive (%)	Hypertensive	59 (56.7)	29 (63.0)	0.586
	Non_Hypertensive	45 (43.3)	17 (37.0)	
Smoker (%)	Non_smoker	69 (66.3)	28 (60.9)	0.644
	smoker	35 (33.7)	18 (39.1)	
SBP (mean (sd))		118.78 (23.19)	117.96 (19.31)	0.834
Heart Rate (mean (sd))		102 (17.36)	104 (14.81)	0.131
location (%)	Anterior	54 (51.9)	23 (50.0)	0.975
	Inferior	41 (39.4)	19 (41.3)	
	Other	9 (8.7)	4 (8.7)	
onset hours (%)	0-4 AM	14 (13.5)	5 (10.9)	0.197
	4-8 AM	21 (20.2)	15 (32.6)	
	8-12 AM	11 (10.6)	7 (15.2)	
	12-4 PM	26 (25.0)	5 (10.9)	
	4-8 PM	22 (21.2)	7 (15.2)	
	8-12 PM	10 (9.6)	7 (15.2)	
complication (%)	Arrhythmia	11 (10.6)	3 (6.5)	0.782
	Cardiogenic Shock	9 (8.7)	4 (8.7)	
	LVF	16 (15.4)	6 (13.0)	
	Recurrent Angina	27 (26.0)	10 (21.7)	
	Uncomplicated	41 (39.4)	23 (50.0)	
adverse_effect (%)	Allergic reaction	5 (4.8)	0 (0.0)	0.407
	hemorrhagic-stroke	2 (1.9)	1 (2.2)	
	minor-moderate bleeding	18 (17.3)	6 (13.0)	
	No adverse effect	79 (76.0)	39 (84.8)	
ST resolution(%)	complete	52(50)	31(67.39)	0.03
	partial	32(30.77)	11(23.9)	
	none	20(19.23)	4(8.7)	

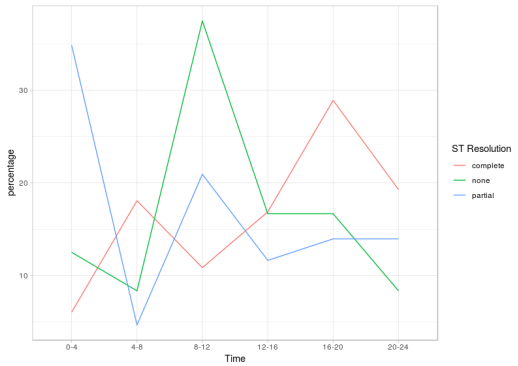
Circadian Variation in the onset of Symptom

There is circadian variation in the onset of symptoms with the peak of onset at 4-8 AM in non-Diabetics(35.45%) in particular which is attenuated in Diabetics. (Fig 1) Ordered Spearman's rank test between the time of onset and Diabetic group revealed a significant negative correlation(r=-0.17, P value=0.03), implying Diabetics had less pronounced morning surge in Myocardial infarction. The variation in the percentage of symptom in Diabetic group was lower than Non-Diabetic group but non-significant. (F ratio=0.22,95%C.I. 0.03-1.56, p value=0.12)



Circadian Variation in the ST resolution on ECG

There is a circadian variation in ST resolution with time- we see that peak in complete ST resolution happened when onset was in the evening 4-8 PM(28.9%) while the peak of no resolution happened when onset was between 4-8 AM(34.88%) (Figure2) There is a significant negative correlation between time of onset of symptoms and complete resolution. (r=-0.21,pvalue=0.007) implying complete resolution is less likely in the early morning.



Comparative Incidence of Complications in thrombolytic groups.

The incidence of complications of Arrhythmia, Cardiogenic shock, LVF and recurrent Angina in streptokinase group was 11/104(10.6%),9/104(8.7%),16/104(15.4%) and 27/104(26%) respectively. The incidence of complications of Arrhythmia, Cardiogenic shock, LVF and recurrent Angina in tenecteplase group was 3/46(6.5%),4/46(8.7%),6/46(13%) and 10/46(21.7%) respectively. The percentage of uncomplicated cases in tenecteplase group 23/46(50%) was non-significantly higher than streptokinase group 41/104(39.4%). (mean difference=10.6%,95% CI= -8.2%-29.3%, pvalue=0.3).

Comparative Incidence of adverse effect in thrombolytic groups.

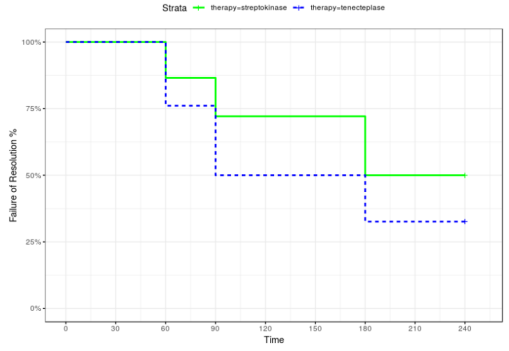
The incidence of complications of allergic reaction, minor-moderate bleeding in the streptokinase group was 5/104(4.8%),18/104(17.3%) respectively. The incidence of minor-moderate bleeding in the tenecteplase group was 6/46(13%) and no allergic reaction was seen. There were two cerebral hemorrhages in the streptokinase group(2/104,1.92%) and one hemorrhage (1/46,2.17%) in the tenecteplase group. The percentage of cases with no adverse effect in tenecteplase group 39/46(84.8%) was similar to streptokinase group 79/104(76%). (mean difference=8.8%,95% CI= -5%-23.6%, pvalue=0.3).

Kaplan Meir Analysis of Hazard

The incidence of complete, partial and no ST-segment resolution in streptokinase group at 180 minutes was 52/104(50%),32/104(30.8%),20/104(19.2%) respectively.The incidence of complete, partial and no ST-segment resolution in tenecteplase group at 180 minutes was 31/46(67.4%),11/46(23.9%),4/46(8.7%) respectively. The incidence of complete, partial and no ST-segment resolution in Anterior wall MI group at 180 minutes was 40/77(51.9%),23/77(29.9%),14/77(18.2%) respectively.The incidence of complete, partial and no ST-segment resolution in Inferior wall MI group at 180 minutes was 37/60(61.7%),17/60(28.3%),6/60(10%) respectively.

Ordered Spearman's rank test between the complete ST resolution(a marker of successful Thrombolysis) and Streptokinase use revealed a significant negative correlation(r=-0.172,95% CI = -0.01 to -0.32, P value=0.03), implying Streptokinase was associated with lower probability of ST resolution.

The hazard ratio(change in probability) of complete ST resolution was significantly higher with tenecteplase than streptokinase (implying tenecteplase is associated with faster complete ST resolution).HR 1.7(95%CI 1.093-2.66, p value=0.02). **(Figure 3)** Median time for complete resolution was 135 minutes in tenecteplase group compared to 180 minutes in streptokinase group.



Discussion

We observed a superior efficacy of complete ST resolution with tenecteplase use as compared to streptokinase in our cohort. There was circadian variation in ST resolution and onset of symptoms which was attenuated in diabetic patients. Side effect profile of Tenecteplase and streptokinase was broadly comparable with the higher percentage of allergic reactions with streptokinase.

Efficacy

The degree of ST resolution is an important marker of short, medium and long-term outcome in myocardial infarction.[12] We evaluated grade of ST resolution at 180 minutes as well to ensure comparability between Streptokinase (given in infusion over an hour) and Tenecteplase(given as bolus) as done in previous studies. Two third of patient had complete ST resolution with tenecteplase while half had complete ST resolution with Streptokinase. A significantly higher number of patients given Tenecteplase had earlier complete ST resolution at 90 and 120 minutes (up to 1.7 times faster HR 1.7) as compared to streptokinase due to its rapid administration. Streptokinase takes time to act and at 180 minutes both agents have similar ST resolution. Faster action of Tenecteplase leads to earlier resolution resulting in shorter median time to complete resolution. While no head to head trials of tenecteplase and streptokinase were done, similar results were seen individuaaly with streptokinase(42%)[13,14]with the percentage of 42% and 60% respectively.[13]

Complications and adverse effects

There was no significant difference in complications during hospital stay despite early ST resolution possibly due to the smaller sample size in our study. Similar findings were seen in TIMI 1 trial [15] Tenecteplase is a more specific fibrinolytic agent and doesn't have antigenic properties like streptokinase which causes immunologic sensitization and allergic reaction. No patient receiving tenecteplase had allergic reaction compared to the incidence of 5% in patients receiving streptokinase. No episode of major bleeding was noted either with streptokinase or tenecteplase, there was only a modest non-significant reduction in minor-moderate bleeding of tenecteplase over streptokinase in our cohort. The incidence of hemorrhagic stroke was around 2% in both groups. These findings reemphasize the importance of streptokinase as a cheap, effective and relatively safe fibrinolytic agent despite its non-specificity. Similar results were seen in ISIS-2 where alteplase didn't have any significant advantage over streptokinase in terms of bleeding side effects. [16]

Circadian variation

We found circadian variation both in the onset of symptoms and severity of disease(as reflected in ST resolution percentage). Morning heart attacks are more frequent and less likely to respond to fibrinolytics. This may be due to increased sympathetic activity and platelet aggregation in the morning which might lead to a disruption of Atherosclerotic Plaques. However, this trend was attenuated in our diabetic patients possibly due to underlying autonomic neuropathy. Similar results were seen in the following studies [17,18]

Our study was a prospective observational study of the non-randomized cohort, which is not ideal for the evaluation of drug effects and was not suitably powered for precisely determining the incidence of adverse effects.

Conclusion

Our study shows that tenecteplase is associated with faster complete ST resolution. Streptokinase has a good safety profile but higher allergic reactions. There is a circadian variation in onset and severity of Myocardial infarction which is attenuated in Diabetic subgroup.

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