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Original Article

Pharmacology Section

Comparative Efficacy between Streptokinase, Tenecteplase and Reteplase in ST Elevated Myocardial Infarction among Patients Attending Tertiary Care Hospital of Odisha

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ABSTRACT

Introduction: ST Elevation Myocardial Infarction (STEMI) is one of the most fatal emergencies contributing to significant morbidity and mortality due to coronary artery disease. Fibrinolytic agents are most effective agents used for the management of STEMI. However, there is a relative paucity of data comparing the effectiveness of thrombolytic agents that can provide insight for proper selection of this class of drugs.

Aim: To compare the efficacy of streptokinase, tenecteplase, and reteplase in patients of STEMI in terms of post-thrombolytic resolution by observing reduction of ST-segment elevation at 90 minutes of thrombolytic and assessing for mortality within 30 days of therapy.

Materials and Methods: This prospective, single-centre, observational, hospital-based study was conducted in the Department of Cardiology in collaboration with the Department of Pharmacology at Srirama Chandra Bhanja Medical College and Hospital, Odisha, India, from February 2020 to January 2022. The study involved 300 patients (100 patients in each group) being treated with streptokinase, or tenecteplase,or reteplase. A reduction of ≥50% of the initial ST elevation was considered as successful thrombolysis. The efficacy of the thrombolysis with these agents was assessed based on the extent of ST resolution in Electrocardiogram (ECG) at 90 minutes and observing 30 day mortality thereafter. Categorical data were evaluated using Chi-square test and the means were evaluated using Analysis of Variance (ANOVA).

Results: There was no statistically significant difference between the three groups with respect to ST segment reduction. At 90 minutes of thrombolysis, 75%, 76%, 72% patients showed reduction in the ST segment in the Streptokinase, Tenecteplase and Reteplase group, respectively (p-value=0.79). A total of nine, five and eight deaths were seen in the streptokinase, tenecteplase and reteplase group, respectively within a span 30 days (p-value=0.52).

Conclusion: Streptokinase, tenecteplase and reteplase were equally efficacious for thrombolysis in terms of thrombus resolution and preventing mortality, when started early.

Keywords: Acute coronary syndrome, Cardiology, Fibrinolytic agents, Mortality, Thrombolysis

INTRODUCTION

Acute Coronary Syndrome (ACS) is a culmination of pathophysiological and clinical changes seen in the myocardium following acute myocardial ischaemia and is one of the most important causes of death globally [1]. Among the various ACS, ST Elevation Myocardial Infarction (STEMI) is a fatal emergency occurring commonly, but can have a lesser effect when treated promptly and appropriately [2]. However, for the treatment to be successful, time of intervention is crucial [3].

Fibrinolytic agents are the most effective agents for the management of STEMI. When administered within 12 hours of onset of symptoms, they can achieve reperfusion and restore blood flow to the infarcted region [4], restore normal cardiac function and can save lives. Fibrinolytic therapy administered within the golden hour can abort Myocardial Infarction (MI) and dramatically reduce mortality. Four fibrinolytic agents are approved by the United States-Food and Drug Administration, namely, streptokinase, alteplase, reteplase and tenecteplase. Streptokinase is one of the safest drugs but being a bacterial extract, it may induce anaphylaxis [5]. Thus, it should not be used again after four days of administration [6]. Subsequent episodes of thrombotic events are thus treated with recombinant tissue Plasminogen Activators (rtPA) such as alteplase, tenecteplase and reteplase [7]. Tenecteplase is administered as a single bolus intravenous injection within 5-10 seconds [8]. It is highly potent but is expensive. Reteplase is administered as a double-bolus regimen, 30 minutes apart. Although it has reduced fibrin selectivity [9], it has a higher coronary reperfusion rate in patients with Acute Myocardial Infarction (AMI) [10].

However, there is a relative paucity of data regarding the efficacy of the various thrombolytic agents in terms of ST segment resolution, coronary reperfusion and short-term mortality in the Indian context. Incidence of acute MI is increasing in an alarming rate in India [11,12]. Fibrinolytic agents like streptokinase, reteplase and tenecteplase are frequently used to manage acute coronary events which save lives when instituted early in therapy. However, recently many recombinant Deoxyribonucleic Acid (rDNA) products have been launched in the market. Streptokinase, being the oldest and cheapest of the above, possess certain demerits in terms of clinical utility. Preliminary surveys found that reteplase and tenecteplase are frequently preferred by the cardiologists/physicians [13,14]. A study by Dasbiswas A et al., reviewed that although primary Percutaneous Coronary Intervention (PCI) was the gold standard treatment, it was not feasible an option many a times in the Indian setting and hence third generation fibrinolytics like reteplase and tenecteplase are emerging as reperfusion strategies to manage STEMI [14]. A network meta-analysis study revealed that tenecteplase and reteplase showed equal efficacy and safety as treatment options for AMI with no significant differences in the parameters such as risk of mortality, TIMI grade 3 flow at 90 mins, infarction or any major bleeding [13]. Tenecteplase has proven to be cost effective and thus, emerged as the fibrinolytic of choice in resource-limited settings [15,16].

Hence, the present study was planned to give a definitive direction to the clinicians about the efficacy of these three thrombolytic agents. The present study aimed to make a head-to-head efficacy comparison between streptokinase, tenecteplase and reteplase used in the tertiary care hospital set-up for the management of STEMI patients in terms of post-thrombolytic resolution by observing reduction of ST segment elevation at 90 minutes of thrombolytic and assessing for mortality within 30 days of therapy.

MATERIALS AND METHODS

This prospective, single-centre, observational, hospital-based, study was conducted in the Department of Cardiology in collaboration with the Department of Pharmacology, at Srirama Chandra Bhanja Medical College and Hospital, Odisha, India, from February 2020 to January 2022. Ethical approval was obtained from the Institutional Ethics Committee of Srirama Chandra Bhanja Medical College prior to the initiation of the study (IEC application no.130).

Sample size calculation: Taking the prevalence of the coronary heart disease at 6% [17,18], precision at 5% and 10% assumed to be a loss to follow-up, a total of 300 patients were recruited, 100 in each group.

Inclusion criteria: Patients of either gender aged >18 years, who presented to the emergency Department or Cardiology Outpatient Department with acute STEMI were included in the study.

Exclusion criteria: Patients undergoing percutaneous coronary intervention were excluded from the study.

ECG was done at the time of admission and those with ST elevation were enrolled after obtaining consent. The patients were treated with streptokinase, tenecteplase or reteplase as preferred by the cardiologists.

Streptokinase group (n=100): The dose of streptokinase administered was 1.5 million units intravenous (i.v.) given over 30-60 minutes.

Tenecteplase group (n=100): Tenecteplase was given as a single i.v. bolus, the dose of which was calculated according to the patient's weight.

Reteplase group (n=100): Reteplase was administered as i.v bolus of 10 units two times at a gap of 30 minutes.

All the study drugs were made available by the hospital free of cost.

Study Procedure

All the enrolled participants were evaluated for demographic and clinical details in a predesigned case record form. The efficacy of the thrombolytic agents was assessed based on the extent of ST resolution in Electrocardiogram (ECG) at 90 minutes of thrombolysis. A reduction of ≥50% of initial ST elevation was considered as successful thrombolysis. The time of presentation to the hospital was evaluated and any admission beyond 12 hours from the onset of symptoms was labelled as delayed presentation. The participants were followed-up for 30 days, from the day of thrombolysis, over phone or when they revisited the Outpatient Department and any death within the aforesaid period was recorded. Repeat ECG was mandated on first follow-up and advised on subsequent follow-ups, if there were signs of infarction [Table/Fig-1].

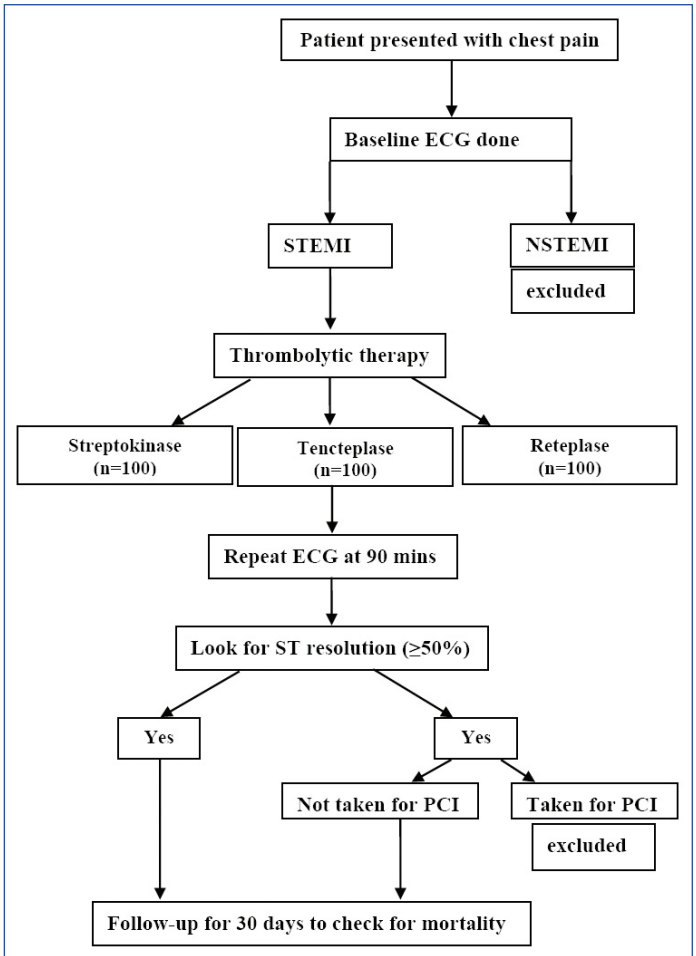
STATISTICAL ANALYSIS

The data was analysed using descriptive statistics like mean and standard deviation, percentages and proportions. Categorical data were evaluated using Chi-square test and the means were evaluated using Analysis of variance (ANOVA). The results were drawn using appropriate statistical tests using Microsoft Excel sheet and Statistical Package for Social Sciences (SPSS) version 20.0. Mortality was assessed using log-rank test.

RESULTS

The baseline characteristics of the participants of all the treating groups were comparable [Table/Fig-2]. The minimum age of the study participants was 37 years and the maximum was 87 years. Most of the patients belonged to the age group of 41-60 years. Diabetes mellitus was the most common risk factor found in the sample.

Anterior wall STEMI was the most common type encountered. There was a significant difference in the time of presentation from the onset of symptoms among the STEMI patients [Table/Fig-3]. There was no statistically significant difference among the three groups with respect to post-thrombolytic ST segment resolution after 90 minutes of the administration of the thrombolytic agent.



[Table/Fig-1]: Flowchart depicting the study procedure.

Variables	Streptokinase (n=100)	Tenecteplase (n=100)	Reteplase (n=100)	p-value
Gender distribution				
Male	66	76	65	0.17*
Female	34	24	35	
Mean age (years)	59.6±8.7	62.3±10.3	59.8±9.0	**0.07**#
Age-group distribution (years)				
20-40	6	3	3	
41-60	61	42	59	
61-80	33	53	38	
>80	0	2	0	
Risk factor profile				
Smoking	35	40	26	0.22*
Tobacco chewing	30	20	24	0.26*
Type 2 diabetes mellitus	53	54	62	0.37*
Hypertension	35	34	53	**0.008***
Dyslipidaemia	27	34	39	0.19*
Alcohol	10	7	6	0.54*

[Table/Fig-2]: Demographic and clinical characteristics of the participants at baseline. *Chi-square test; #ANOVA; p-value <0.05 was considered as statistically significant

Parameters	Streptokinase (n=100)	Tenecteplase (n=100)	Reteplase (n=100)	p-value (Chi-square test)
Types of STEMI				
Anterior wall STEMI	45	41	43	0.32
Inferior wall STEMI	25	18	16	
Others	30	41	41	
Window period				
<12 hours	35	53	31	**0.003**
>12 hours	65	47	69	
ST-segment resolution at 90 mins				
Yes	75	76	72	0.79
No	25	24	28	
30 day mortality	9	5	8	
≤1 day	4	3	3	0.52
2-7 days	4	2	4	
8-30 days	1	0	1	

[Table/Fig-3]: Outcomes of the study.
p-value <0.05 was considered as statistically significant; p-value*: Chi-square test

Most number of deaths occurred either within the first 24 hours or first week of thrombolysis. Maximum number of deaths within 24 hours was seen with streptokinase, followed by tenecteplase and reteplase.

The association between smoking and co-morbidities like diabetes and hypertension with ST segment resolution (hence the outcome of thrombolysis) was also, studied. A comparison of ST resolution at 90 mins between smokers and non smokers, diabetics and non diabetics, and hypertensives and non hypertensives was made in all the three arms. There was no statistically significant difference among the aforesaid groups in any of the treatment groups [Table/Fig-4].

As evident from [Table/Fig-3], the number of study participants who presented before and after 12 hours of onset of symptoms varied significantly (p-value=0.003). Within groups comparison in all the three treatment groups, showed no statistically significant difference in ST resolution at 90 mins between those who presented before and after 12 hours of onset of symptoms.

The intragroup comparison of success of thrombolysis with streptokinase, tenecteplase and reteplase was found to be similar in patients presenting before and after 12 hours in the respective arms [Table/Fig-5]. [Table/Fig-6] depicts an intergroup comparison where the success of thrombolysis (defined by ≥50% ST resolution at 90 mins) was compared among the patients presenting before and after 12 hours of onset of symptoms in the three treatment arms, separately. In both the above scenarios, results were statistically non significant. The estimated 30-day survival in tenecteplase group was 94.5% followed by reteplase (91.3%) and streptokinase (90.7%). There was no significant difference between the treatment arms (log-rank test; p=0.96) [Table/Fig-7]. This data is further supported by the Cumulative hazard function, which was 0.05 in tenecteplase group, followed by 0.09 in reteplase group, and 0.99 in the streptokinase group. This implied that the risk of death after 30 days of treatment was least with tenecteplase.

DISCUSSION

The study focused on three thrombolytic agents commonly prescribed in the study set-up, namely, streptokinase, reteplase and tenecteplase. The aim was to evaluate their efficacy in terms of ST segment resolution ≥50% of initial rise and mortality up to 30 days of thrombolysis. This study found no significant difference in the aforesaid parameters among the three agents used. In the present study, there was a significant difference in the number of patients turning up with early (<12 hours) and delayed (>12 hours) presentations.The primary outcome was to assess the success

Associated conditions	ST resolution at 90 minutes after thrombolysis								
	Streptokinase			Tenecteplase			Reteplase		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Smokers	26 (74%)	9 (26%)	0.59	30 (75%)	10 (25%)	0.84	19 (73%)	7 (27%)	0.88
Non smokers	45 (69%)	20 (31%)		46 (76%)	14 (24%)		53 (72%)	21 (28%)	
Diabetics	36 (68%)	17 (32%)	0.22	40 (74%)	14 (26%)	0.62	45 (73%)	17 (27%)	0.86
Non diabetics	37 (79%)	10 (21%)		36 (78%)	10 (22%)		27 (71%)	11 (29%)	
Hypertensives	25 (71%)	10 (29%)	0.79	26 (76%)	8 (24%)	0.93	37 (70%)	16 (30%)	0.60
Non hypertensives	48 (74%)	17 (26%)		50 (76%)	16 (24%)		35 (74%)	12 (26%)	

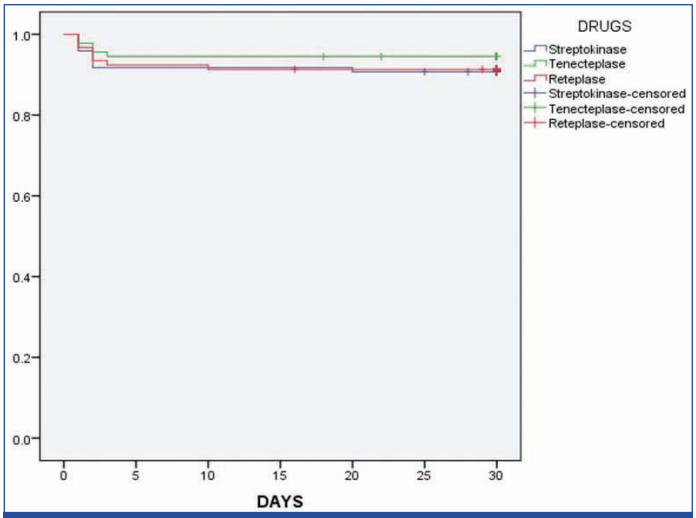
[Table/Fig-4]: Outcome of thrombolysis in different groups Chi-square test used.

Time of presentation	ST resolution at 90 minutes after thrombolysis								
	Streptokinase			Tenecteplase			Reteplase		
	Yes	No	p-value*	Yes	No	p-value*	Yes	No	p-value
<12 hours	25 (71%)	10 (29%)	0.66	38 (72%)	15 (28%)	0.28	23 (74%)	8 (26%)	0.74
>12 hours	49 (75%)	16 (25%)		38 (81%)	9 (19%)		49 (71%)	20 (29%)	

[Table/Fig-5]: Within group ST resolution with respect to time of presentation to the hospital.
Chi-square test used

ST resolution at 90 minutes after thrombolysis	Time of presentation <12 hours			p-value
	Streptokinase (n=35)	Tenecteplase (n=53)	Reteplase (n=31)	
Yes	25 (71%)	38 (72%)	23 (74%)	0.96
No	10 (29%)	15 (28%)	8 (26%)	
ST resolution at 90 minutes after thrombolysis	Time of presentation>12 hours			
	Streptokinase (n=65)	Tenecteplase (n=47)	Reteplase (n=69)	p-value*
Yes	49 (75%)	38 (81%)	49 (71%)	0.48
No	16 (25%)	9 (19%)	20 (29%)	

[Table/Fig-6]: Between-group ST resolution with respect to time of presentation to the hospital.
Chi-square test used



[Table/Fig-7]: Kaplan-Meier curve showing mortality within 30 days.

of thrombolysis, defined by ST segment resolution ≥50% of initial rise, within each treatment group (intragroup) as well as between the three treatment options (intergroup) with respect to the time of presentation. The end results were similar and there was no significant difference in the outcome of thrombolysis (p-value >0.05).

In the present study, the most common site of infarction was in the anterior wall i.e. AW-STEMI. Studies by Pandey R et al., [19] and Hashmi SF et al., [20] found that IW-STEMI are more common than AW-STEMI. Anteroseptal MI was found to be the most prevalent MI in a study by Mohammed OS et al., followed by inferior wall MI and anterior wall MI [21]. Irreversible injury occurs within 2-4 hours of ischaemia, hence thrombolysis is most effective in the first two hours. Thrombolytic therapy after 12 hours of the onset of symptoms increases the risk of intracranial bleeding out weighing any benefit [22,23]. In the present study, 60% of the presentations were after 12 hours and only 40% presented before 12 hours. A study by Lakshmi NR et al., showed that earlier the thrombolysis, better the success rate it holds [23]. When thrombolysis was done within 3 hours, the success rate was 51.4% compared to 3-6 hours and >6 hours, where the rate of success reduced to 34.3% and 14.3%, respectively. It is a common clinical observation that diabetic subjects have diminished pain perception and hence, higher chances of asymptomatic infarctions. Among the diabetics, 40% presented within 12 hours and among the non diabetics, it was 42%. The results corroborate with another study by Kentsch M et al., which found that there appears to be no difference in clinical symptoms of AMI in patients with or without diabetes. AMI with little or no angina was also frequently found in non diabetics [24]. A qualitative study by Berman N et al., showed that attenuated symptoms in MI among people with diabetes mellitus often led to delay in seeking attention and hence, a delay in receiving treatment [25].

The overall success rate of thrombolysis with streptokinase, tenecteplase and reteplase was 75%, 76% and 72%, respectively. A retrospective study done by Lee YY et al., on 192 patients concluded that streptokinase had a failure rate as high as 56.8% [26]. It also stated that history of diabetes mellitus, hypertension and longer door-to-needle time were predictive factors for the therapeutic failure of streptokinase. This was in contrast to the index study where association of co-morbidities like diabetes mellitus, hypertension did not affect the overall outcome of thrombolysis (p-value >0.05). Another study by Girdhar DR et al., done on 104 patients found a success rate of 67.3% with streptokinase [27]. A study by Srinivasan K, revealed 54% of successful thrombolysis with streptokinase [28]. Also, the rate of success was more among non smokers as compared to smokers. This was in contrast with the present study, where smoking had no role to play in the success or failure of the treatment, with thrombolytics.

Tenecteplase had a success rate of 76% in the present study. This was in line with other studies where tenecteplase showed a very high success rate. A study by Iyengar SS et al., done with 6000 study participants showed a success rate as high as 90.93% [29]. Another study with 2162 study participants also proved a high count of successful thrombolysis with tenecteplase i.e. 83.9% [30]. In the present study, tenecteplase was found to have the highest 30-day survival rate (94.5%) among all the three thrombolytics. This corroborated with a study by Chua KW et al., where the group receiving tenecteplase had greater survival rate, at 30 days and overall mortality [31]. The overall success rate was 79% which was similar to the findings of the present study.

Reteplase had a success rate of 72% and the estimated 30-day survival was 91.3%, second to tenecteplase. A study by Singh RK et al., on 228 patients revealed a successful thrombolysis in 90.5% of study participants with IV reteplase [32]. The 30-day survival rate of reteplase was equivalent to that of streptokinase in the present study. This finding corroborated with a study (INJECT study) where 35-day survival rate was evaluated on 5986 patients, and it too revealed, that double bolus (10U+10U) administration of reteplase was equivalent to one hour infusion of 1.5 million units of streptokinase [33].

The present study also evaluated, if there was any difference in the time of presentation among smokers and non smokers with acute MI and observed no significant difference (p-value=0.15). In the present study, the post-thrombolytic resolution in the three groups i.e., streptokinase (75%), tenecteplase (76%) and reteplase (72%) were comparable. A study at Telangana by Guha S et al., revealed that reteplase was the safest and most efficacious in resolution of ST elevation [34]. In another study by Siddiquei MA et al., tenecteplase was found to be superior to streptokinase in terms of faster complete ST resolution [35]. The study showed that there was no significant difference in ST segment resolution among smokers versus non smokers, diabetics versus non diabetics or hypertensives versus non hypertensives. In a study by Wong CK et al., there was reduced effectiveness of thrombolytic therapy in diabetic patients versus non diabetic patients [36].

In the present study, the overall mortality was 9% in streptokinase group, 8% in reteplase group, and 5% in tenecteplase group. A meta-analysis showed that the use of thrombolytic agents significantly reduces the mortality at 30 days of thrombolysis [37]. In the present study, there was no significant difference in mortality between the three treatment arms. Similar results were found in a study, where they compared tenecteplase, reteplase, and accelerated alteplase. In a study by Mega JL et al., women undergoing fibrinolysis for STEMI, were at a higher risk of short-term mortality [38].

Limitation(s)

Since, the study was aimed to evaluate the efficacy of these thrombolytic agents for an acute event, the safety profile could not be studied due to short hospital stay. Further, a well-planned cost effective analysis could have been implemented to add to the conclusion, which is in process. Future studies on safety profile of the different thrombolytic agents used and long term mortality with higher sample size can give a clearer picture.

CONCLUSION(S)

Streptokinase, tenecteplase and reteplase are equally efficacious with respect to ST resolution and 30-day mortality among the patients of ST elevation myocardial infarction in the study set-up and judicious use of these thrombolytic agents at proper time, can save precious lives.

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