



SAFETY AND EFFICACY OF STREPTOKINASE, RETEPLASE AND TENECTEPLASE IN PATIENTS WITH ACUTE STELEVATEDMYOCARDIAL INFARCTION IN AN INTENSIVE CARDIAC CARE UNIT OF A TERTIARY CARE TEACHING HOSPITAL

**RANAKISHORE PELLURI¹, VANITHA RANI N ^{*2}, M. RAMESH ³,
G. KANNAN⁴ AND P. THENNARASU⁵**

³*Department of Cardiology, Sri Ramachandra Medical Center.*

^{*2, 1, 3, 4}*Department of Pharmacy Practice, Sri Ramachandra College of Pharmacy
Sri Ramachandra University, Chennai- 600116, INDIA.*

ABSTRACT

Although streptokinase and tissue plasminogen activators tenecteplase, reteplase and alteplase are in clinical use for Acute ST-segment elevated myocardial infarction (STEMI), their efficacy in reducing mortality and safety remains less explored. A study was conducted in 90 patients of either sex (30 patients each in streptokinase (SK), tenecteplase (TNK) and reteplase (RTP) groups), aged above 18 years, admitted with acute STEMI in the Intensive Coronary Care Unit to assess the efficacy and safety of fibrinolytics. Data on efficacy and safety parameters before and after the initiation of therapy were obtained from patient medical records and were assessed. Based on the efficacy parameters, 27 patients in SK and RTP group each and 26 in TNK group had more than 50 % resolution; no early peaking in 3 patients each in SK and RTP & one in TNK group; reperfusion arrhythmia was noted in one patient each in SK & TNK; but no arrhythmias in RTP group; symptoms relief < 50% in 5 patients in TNK; 2 in SK & one in RTP treated group; re-MI in one patient in TNK group. Based on the safety parameters, one patient each developed anaphylaxis and hypotension in the SK group, one had CVA in TNK group and no ADRs were identified in RTP group; survival rate was 100% in RTP group and 96.7 % in SK and TNK groups each. The above study identified reteplase as more safe and efficacious than Streptokinase and Tenecteplase.

KEY WORDS: fibrinolysis, STEMI, reperfusion, tissue plasminogen activator



VANITHA RANI N

Department of Pharmacy Practice, Sri Ramachandra College of Pharmacy
Sri Ramachandra University, Chennai- 600116, INDIA.

INTRODUCTION

Coronary artery disease (CAD) is the single most frequent cause of death worldwide and over seven million people every year die from CAD, accounting for 12.8% of all deaths. The burden of CAD is predicted to be greatest in India and according to the estimates from the Global Burden of Disease Study of more than 9 million deaths due to CAD in 1990 in developing countries, 2.4 million (25%) occurred in India. In the same year, mortality rates in India due to acute myocardial infarction (MI) were 141 per 100,000 in males and 136 per 100,000 in females, which was much higher than in China (66 per 100,000 in males and 69 per 100,000 in females) and Latin American countries (81 per 100,000 in males and 76 per 100,000 in females). In Indians, the overall cardiovascular mortality is predicted to rise by 103% in men and 90% in women between 1985 and 2015. The most alarming matter of concern is that 52% of the CAD deaths in India occurred in people aged below 70 years, while the same was just 22% in developed countries¹. Worldwide around 7 million people suffer myocardial infarction per year. Around one third of these patients having an acute myocardial infarction (MI) die within the first hour of having symptoms usually due to fatal arrhythmias. The most reliable and a rapid way of diagnosing patients for thrombolysis and timely restoration of blood flow is a characteristic elevation in the ST segment in a 12 lead electrocardiogram (ECG) accompanied by complaints of chest pain. Thrombolysis is considered as the cornerstone of therapy for patients with ST segment elevation myocardial infarction (STEMI) since three decades as it not only improve the outcomes but also preserves the left ventricular function. A large randomised clinical trials like Fibrinolytic Therapy Trialists' (FTT) Collaborative Group also emphasises the significance of early reperfusion with 30 lives per 10000 being saved if thrombolysis given within 6 hours of presentation and 20 lives per 1000 saved if initiation is between 6 and 12 hours². The management of acute myocardial infarction by pharmacological reperfusion therapy was incorporated into the armamentarium of clinicians over a decade ago and has proven to have an remarkably

positive impact on the prognosis of patients with acute ST-elevation myocardial infarction³⁻⁵. Three fundamental components to pharmacological reperfusion are the core fibrinolytic agents and the accompanying antithrombotic and antiplatelet conjunctive therapies. Various multiple large randomized trials have comprehensively examined the efficacy, safety, and impact of newer third-generation fibrinolytics and advances in conjunctive therapies aimed at enhancing restoration of myocardial flow in the epicardial infarct-related coronary artery. An overview of the origin of thrombolytic therapy, starting from recognition of the "fibrinolytic" potential of b-hemolytic streptococci to the revelation of the ability of streptokinase (SK) to dissolve an established blood clot and fibrinous exudates in a patient with a hemothorax was given by Sherry⁶ a pioneer in fibrinolysis. It took 25 years for this discovery to end up in the application of SK treatment for people with acute myocardial infarction and another quarter of a century before the life-saving potential of streptokinase (SK) for this life threatening condition was clearly established. However factors like allergic reactions to bacterial proteins in streptokinase and the risk of hemorrhage induced by a systemic fibrinolytic state remained the major concern of medical community towards the use of streptokinase⁷. The recent and the most conveniently administered bolus fibrinolytics are the tissue plasminogen activator (tPA) congeners tenecteplase (TNK-tPA) and reteplase (rPA) which possess initial plasma half-lives of 15 to 30. Apart from reducing the potential for medication errors they also greatly simplify the prospects of prehospital fibrinolysis^{3,4}. The 'first generation' thrombolytics had clinical disadvantages such as low specificity for fibrin, increased risk of allergic reactions (in particular with streptokinase) and short half-life. Newer thrombolytic agents such as Alteplase, Reteplase and Tenecteplase have been developed with potential advantages that include: a longer half-life, high fibrin specificity and an increased resistance to inhibition by plasminogen activators. However, these laboratory-measured advantages may not

translate into measurably beneficial clinical outcomes. An increased incidence of intracranial haemorrhage had resulted in the withdrawal of the new thrombolytic drug lanoteplase from development^{8,9}. Globally, fibrinolytic therapy with streptokinase and tissue plasminogen activators tenecteplase, reteplase and alteplase has profound impact on the management of patients with acute ST-

segment elevation myocardial infarction. The ability of these agents to achieve rapid and effective coronary reperfusion as a systemic intravenous bolus or infusion has truly transformed therapeutic approach^{10,11}. Although these drugs are in extensive clinical use, their efficacy in reducing mortality and safety needs to be explored further in different patient population.

METHODOLOGY

Study design A comparative observational study

Study population & Size

A total 90 patients of either sex, admitted with acute STEMI in the Intensive Coronary Care Unit of a tertiary care teaching hospital and were administered with Streptokinase, Reteplase & Tenecteplase (30 patients each)

Inclusion criteria

1. Age \geq 18 years
2. Onset of symptoms \leq 12 hours
3. ST-segment elevation of \geq 0.1 mV in \geq 2 limb leads or \geq 0.2 mV in \leq 2 contiguous pre cordial leads, or acute onset left bundle-branch block.

Exclusion criteria

Absolute

1. Prior intracranial hemorrhage
2. Known structural cerebral vascular lesion
3. Known malignant intracranial neoplasm
4. Ischemic stroke within 3 months
5. Suspected aortic dissection
6. Active bleeding or bleeding diathesis (excluding menses)
7. Significant closed- head trauma or facial trauma within 3 months

Relative

1. Uncontrolled hypertension (systolic BP $>$ 180 mm Hg or diastolic BP $>$ 110 mm Hg)
- 2.Underwent a major surgery or prolonged cardiopulmonary resuscitation (CPR) or had been traumatised within 3 weeks
- 3.History of internal bleeding in 2-4 weeks
- 4.Non-compressible vascular punctures
- 5.Previous exposure to streptokinase (in a short span) or history of hypersensitivity to streptokinase
6. Pregnant women, lactating mothers, or women who had parturition in the past 30 days
7. Subjects participating in any other investigational drug or device study
- 8.Active peptic ulcer
- 9.Current use of warfarin and INR $>$ 1.7

Parameters assessed

Efficacy monitoring parameters

- 1.ST-Segment resolution ($>$ 50%)
- 2.Peaking of cardiac enzymes: CPK/CPK MB
- 3.Reperfusion arrhythmias
- 4.Time to symptoms relief ($>$ 50%)

- 5.Re MI
- 6.Mortality

Safety monitoring parameters

- 1.Hypotension
- 2.Bleeding
- 3.Allergy (anaphylaxis)
- 4.CVA (cerebro vascular accident)

Methods

A prospective, observational, study was conducted in a total of 90 patients with acute ST-segment elevated myocardial infarction and administered with fibrinolytics Streptokinase, Reteplase & Tenecteplase. The study population was divided into 3 groups based on the fibrinolytic drug received as SK group, tenecteplase group and reteplase group containing 30 patients in each group. The study was conducted with the approval of the Ethics Committee and consent of the study population.

Data collection

Data including patient demographics (age, sex, BMI), past medical and medication history, family history, diagnosis and laboratory investigations (CPK, CPK-MB, Troponin T) & ECG, fibrinolytic therapy given (Streptokinase, Reteplase & Tenecteplase) were obtained from patient case records and by direct medical history interview for patients in all three groups and documented in the data collection proforma specially designed for the study. The details of the efficacy parameters such as ST-Segment resolution (>50%), Reperfusion arrhythmias, subsiding of pain/ symptoms, were obtained from patients' ECG, and cardiac markers such as CPK, CPK-MB and Troponin T values were obtained from laboratory reports. The details of Re MI, time to symptoms relief and mortality were obtained from patient medical records. Prognosis, treatment-related adverse reactions (major and minor bleeding, hypotension, anaphylaxis, CVA) and mortality rate were recorded. Death due to all causes, ST-segment resolution, pain disappearance,

and adverse reaction rate were considered as the primary endpoints. The safety parameters such as hypotension, bleeding, allergy and CVA were obtained from patient's medical records. The efficacy and safety parameters were assessed before and after the initiation of therapy for the patients in the three groups and were tabulated and expressed in descriptive statistics and Chi-square test. A p-value < 0.001 was considered as statistically significant.

RESULTS

A total number of 90 patients {77 males (85.5%) & 13 females (14.5 %)} who have been admitted with ST segment elevation acute MI, in the Intensive Coronary Care Unit (ICCU), were monitored for the efficacy and safety of fibrinolytic therapy (Streptokinase, Reteplase & Tenecteplase). The age range of study population was 25 to 75 years (Mean age \pm SD was 52.9 ± 12.3 years). Majority (49%) of the patients were in the age range of 46-60 years. The range of BP on admission was 60/40 mmHg to 170/120 mmHg (Mean BP \pm SD, 110 ± 70 mmHg/ 72 ± 14 mmHg). The BMI range of the study population was found to be 20.1 to 31.25 kg/m² (Mean BMI \pm SD of 25.01 ± 2.13 kg/m²). Majority of the patients (56.66%) were overweight with a BMI range of 23-25 kg/m², followed by 26.66% of patients being obese with the BMI range of 26 -30 kg/m². Of 90 patients, 25 (27.7%) were smokers, 24 (26.6%) were alcoholics, 2 (2%) were tobacco users and 3 (3%) had allergies (Table 1)

Table No 1
Baseline Characteristics of Study Population

Characteristics	No. of Patients	%
Age range (years)		
18 – 30	7	7.8
31- 45	16	17.8
46 – 60	44	48.9
> 60	23	25.6
BMI range (kg/m ²)		
18-22 (Normal)	14	15.6
23-25 (Overweight)	51	56.7
26 -30 (Obese)	24	26.7
31 -35 (Obese –Grade I)	1	1.11
Smoking	25	27.7
Alcoholism	24	26.6
Tobacco/Illicit Drugs	2	2.2
Allergies	3	3.3

The fibrinolytic therapy given for the patient was described in table no 2. Of 90 patients, 30 (33.33%) patients were prescribed with streptokinase; 30 (33.33%) were prescribed with tenecteplase and 30 (33.33%) were prescribed with reteplase.

Table No 2
Fibrinolytic Drugs Used

S. No	Fibrinolytics	No. of patients		Total No of patients (N=90)	Percentage (%)
		males (n=30)	females (n=30)		
1	Streptokinase (SK group)	23	7	30	33.33
2	Tenecteplase (TNK group)	27	3	30	33.33
3	Reteplase (RTP group)	27	3	30	33.33

Table 3 shows the efficacy & safety parameters of the patients prescribed with Streptokinase, tenecteplase and Reteplase. The parameters monitored for efficacy were ST segment resolution (> 50 %), early peaking of CPK, CPK-MB (> 50 %), Reperfusion arrhythmias, Time to symptoms relief (>50 %), Re occurrence of MI and Mortality.

Efficacy of three thrombolytics

- Of 30 patients in the SK group, 3 patients had < 50% ST-segment resolution, and the remaining 27 had more than 50 % resolution. Of 30 patients in the reteplase group, 3 patients had < 50% ST segment resolution and the remaining 27 had more than 50 % resolution. Of 30 patients in the TNK group 4 patients had < 50 % resolution. {SK,RTP > TNK}
- Early peaking was not found in 3 patients treated with SK, 3 patients with RTP & one patient with TNK.{TNK > SK,RTP}

- Reperfusion arrhythmias were noted in one patient in each group of SK & TNK; but no arrhythmias were found in patients treated with RTP {RTP > SK, TNK}
- Symptoms relief < 50% were found in 5 patients treated with TNK; 2 patients with SK & one patient with RTP treated group. {RTP > SK > TNK}
- Re-MI was observed in one TNK treated patient. {SK, RTP > TNK}

Safety of three thrombolytics

The safety parameters were observed in all three groups of patients. The parameters monitored for safety were; Hypotension, bleeding, allergy (Anaphylaxis), Cerebro Vascular Accident (CVA) & Mortality.

- One patient in the SK group developed anaphylaxis and one patient had hypotension. {RTP, TNK > SK}
- One patient had CVA among patients with TNK. {SK, RTP > TNK}
- No ADRs were identified in group of 30 patients treated with RTP. {RTP, SK > TNK}
- Survival rate was 100% in RTP treated group and 96.66% in groups treated with SK & TNK respectively.

Table No 3
Overall efficacy, safety and mortality of SK, TNK & RTP Group

Parameters	SK (n=30)		TNK (n=30)		RTP (n=30)	
	n	%	N	%	N	%
EFFICACY PARAMETERS						
ST segment resolution > 50 % after lysed	27	90	26	86.66	27	90
Early peaking (CPK, CPK-MB)	27	90	29	96.66	27	90
Reperfusion Arrhythmias	1	3.33	1	3.33	0	0
Symptoms relief > 50 %	28	93.33	25	83.33	29	96.66
Re MI	0	0	1	3.33	0	0
Mortality	1	3.33	1	3.33	0	0
SAFETY PARAMETERS						
Hypotension	1	3.33	0	0	0	0
Bleeding	0	0	0	0	0	0
Allergy (anaphylaxis)	1	3.33	0	0	0	0
CVA	0	0	1	3.33	0	0
GENERAL PARAMETERS						
Males	23	76.66	27	90.00	27	90.00
Females	7	23.33	3	10.00	3	10.00
Patients with history of drug Allergies prior to MI therapy	0	0	2	6.66	0	0
Smokers	10	33.33	6	20.00	10	33.33
Alcoholics	9	30.00	6	20.00	9	30.00
Co morbidities	22	73.33	22	73.33	22	73.33
T2DM + HTN	21	70.00	19	63.33	14	46.66
Patients underwent for PTCA	1	3.33	1	3.33	0	0
Patients treated with GPIIa/IIIb	0	0	1	3.33	1	3.33

Table 4 shows the overall efficacy & safety parameters of the patients prescribed with Streptokinase, Tenecteplase and Reteplase.

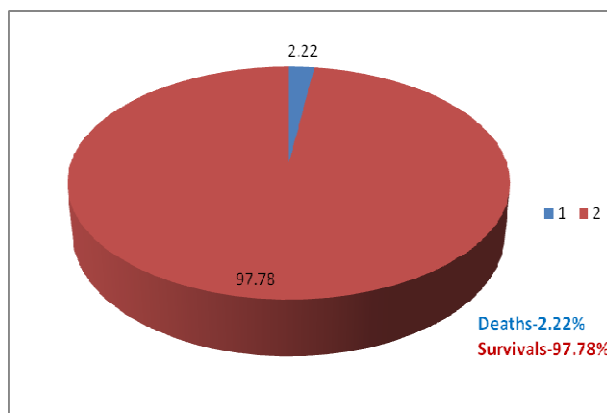
- The percentage of efficacy was high in patients treated with RTP (93.3%) ; where as in SK treated patients was 86.7% and 80% of efficacy was observed in patients treated with TNK. {RTP > SK > TNK}.
- The percentage of safety was high in both RTP 96.7% & TNK 96.7% treated patients; where as in SK treated patients safety (93.3%) was less when compared with RTP & TNK treated patients. {RTP > TNK > SK}.

Retepase had a highly significant efficacy and no mortality when compared to streptokinase and tenecteplase (p <0.001). But the safety parameter was same as that of tenecteplase but highly significant when compared to streptokinase (p<0.001).

Table No 4
Comparison of Safety, efficacy and Mortality of Streptokinase, Tenecteplase & Reteplase

Drug Name	Efficacy %	Safety %	Mortality %	p-Value
RTP	93.3	96.7%	0%	0.001** (** p-value <0.001)
SK	86.7	93.3%	3.33%	
TNK	80.0	96.7%	3.33%	

Figure 1
Survival and Death Rate of Patients



- 100% survival rate was found in patients treated with RTP, and 96.66% survival rate was found in patients treated with both SK & TNK. {RTP > SK & TNK}.The overall survival rate of the study population was found to be 97.78% (Fig:1).
- In this comparative study there was an equal number & percentage (22 & 73.33%) of co morbidities either T2 DM or HTN or both in all three group of patients.
- The total number & percentage of patients thrombolysed after symptoms onset of < 12 hours was 29 (96.66%) in SK treated group.
- All 30 patients were thrombolysed after symptoms onset of < 12 hours in RTP & TNK treated groups.
- Door to needle time was < 30 min in 9 (30%) patients with SK, 13 (43.33%) patients in RTP group and in 14 (46.66%) patients in TNK group.
- There was one patient each in SK & TNK group who had undergone PTCA after being thrombolysed.

- The adjunctive therapy with GPIIb/IIIa receptor antagonist TIROFIBAN 5mg/100 ml was given after being thrombolysed for one patient each in RTP in TNK group. The patient treated with RTP and Tirofiban developed severe immune thrombocytopenia.

DISCUSSION

Fibrinolytic therapy has become the mainstay of treatment for acute transmural myocardial infarction. A comparative study was conducted to assess the efficacy and safety of fibrinolytic drug therapy (Streptokinase, tenecteplase, reteplase) for 90 patients with acute STEMI. Streptokinase was administered for 30 patients; tenecteplase was given for 30 patients and reteplase was given for 30 patients for fibrinolysis. Based on the efficacy monitoring parameters, ST segment resolution of > 50% was observed in 90% of patients with both streptokinase and reteplase treated patients.

1. 27 patients with SK & RTP had > 50 % ST segment resolution out of 30 patients respectively where as 26 patients with TNK had > 50 % ST segment resolution out of 30 patients. The study observed that SK & RTP had good ST segment resolution than TNK. {SK & RTP > TNK}
2. Early peaking of CPK, CPK-MB in patients treated with SK (90%) & RTP (90%) were found to be less as compared with TNK (96.66%) group { TNK > SK, RTP}.
3. Reperfusion arrhythmia was found in one SK & one TNK treated patients. No patients treated with RTP had Reperfusion arrhythmias.
4. Symptoms relief was better in patients with RTP (96.66%) , followed by SK (93.33%) as compared with TNK (83.33%) group {RTP > SK > TNK}

In the last decade, several observations have led to a reappraisal of the utility of ST segment monitoring after ST elevation MI (STEMI). Schroeder and colleagues showed that ST segment resolution can predict accurately the risk for death and congestive heart failure (CHF) in patients treated with fibrinolytic therapy. Resolution of ST segment elevation is now being used with increasing frequency in determination of prognosis early after fibrinolytic therapy and direct comparison of different reperfusion regimens^{12,13}.

In the present study monitoring of the safety parameters of SK, TNK & RTP were as follows:

1. The occurrence of anaphylaxis was in 3.33% & hypotension in 3.33% of patients with streptokinase.
2. Re-MI was found in one patient (3.33%) treated with TNK.
3. CVA was found in one patient treated with TNK.
4. 100% survival rate was found in patients treated with RTP as compared to SK (96.66%) & TNK (96.66%) groups {RTP > SK, TNK}.

The effectiveness of thrombolytic therapy is greatly diminished in the presence of severe hypotension. The GISSI- I trial showed a very high mortality rate associated with Killip class N, and a lack of improvement with streptokinase therapy in these patients (mortality rates of 69.9% with streptokinase and 70.1% with placebo)¹⁴. In a study done by Gruppo Italiano 1986, in PIT (Pulse Infusion Thrombolysis) overview, patients with both a systolic pressure of less than 100 mm Hg and a heart rate exceeding 100 beats/min were also at high risk of death¹⁵. Streptokinase is a first generation fibrinolytic with a plasma half-life of approximately 25 minutes. It acts by

binding to plasminogen, forming a streptokinase-plasminogen complex that converts plasminogen to plasmin, which initiates fibrinolysis. Streptokinase is not fibrin-specific and activates both circulating and clot-bound plasminogen, which leads to systemic lysis of fibrin. The systemic plasminogen activation with streptokinase results in extensive fibrinogen depletion and concomitant bleeding risks. Major disadvantage of streptokinase is that some patients develop antibodies to it (preventing its reuse), and allergic reactions, hypotension and bleeding as a result of its non-specific plasminogen binding¹⁶. In the present study,

only one patient with streptokinase developed anaphylaxis and none reported hypotension or bleeding. Reteplase and tenecteplase are third generation fibrinolytics. Reteplase (r-PA; Retavase) is a deletion mutant of tissue plasminogen activator that preferentially activates fibrin-bound plasminogen. It has a half-life of approximately 11 minutes¹⁷. Tenecteplase (TNK-t-PA; TNKase), a triple mutant of tissue plasminogen activator, is more specific than alteplase for fibrin, more resistant to PAI-1, and longer-lasting (with a half-life of approximately 20 minutes). Owing to its long half-life, tenecteplase can be given as a single bolus¹⁸⁻²¹. The above study identified reteplase as the more safe and efficacious fibrinolytic agent as compared to SK & TNK. This may not suggest reteplase to be superior over the other two drugs as there are limitations such as a lesser sample size of the three groups, the cost effectiveness ratio of three drugs. Despite the survival benefit of these agents, data have suggested that many potential candidates for fibrinolytic therapy are not receiving it²¹. These agents should be considered in all patients presenting with ST-elevation MI. The recommended guideline of door to needle time of 30 min is observed in the minority of all the groups. If these guidelines are adhered to better results with thrombolytics can be anticipated. Most patients in this study were arrived within a shorter time window; if they have arrived within a shorter window thrombolysis would be more beneficial.

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CONCLUSION

The study was conducted to assess the efficacy and safety of streptokinase, tenecteplase and Reteplase used in the fibrinolytic therapy of patient with acute STEMI. The total 90 patients were included in the study, each group having 30 patients. The study identified all three fibrinolytic drugs to be efficacious in causing > 50% resolution in ST segment, peaking rate & symptoms relief. In terms of efficacy the RTP (93.33%) was good as compared to SK (86.77%) & TNK (80.00%) the p-value was <0.001 {RTP > SK > TNK}. There was one patient with hypotension (3.3%) in SK treated group and one patient had anaphylaxis with SK. CVA (3.3%) was found in one patient with TNK treated group. The overall safety was equal for both RTP (96.70%) & TNK (96.70%) groups as compared to SK (93.30%) treated patients {RTP & TNK > SK}. There were two patients (one RTP & one TNK) who received adjunctive therapy with tirofiban, in that patient on RTP ± Tirofiban had developed severe thrombocytopenia (3.3%). There were two (one SK & one TNK) patients who had undergone PTCA after thrombolysis. Re-MI was observed in one TNK (3.3%) treated patient & was not found in any of the SK & TNK treated groups. The survival rates were 96.66% in both SK & TNK treated group and 100% in RTP group. The mortality rates were 3.33% in both SK & TNK treated group and 0% in RTP group

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