Original Article

Safety and Efficacy of Streptokinase, Tenecteplase, and Reteplase in Patients Diagnosed with ST-Elevation Myocardial Infarction: A Comparative Study

Bhargavi Neela, Vineeth Reddy Gunreddy, Mamatha Reddy Chandupatla[1], Venkateshwarlu Eggadi, Sheshagiri Sharvana Bhava Bandaru

Department of Clinical Pharmacy and Pharm.D., Vaagdevi College of Pharmacy, [1]Department of Cardiology, Kakatiya Medical College, Mahatma Gandhi Memorial Hospital, Warangal, Telangana, India

Abstract

Objective: Our primary objective was to compare the efficacy of streptokinase (SK), tenecteplase, and reteplase by studying patients' electrocardiogram Electrocardiogram(ECG) pre and post thrombolysis. The secondary objectives were to assess chest pain relief using Numerical Pain Rating Scale score and also to compare the side effects (bleeding, hypotension, and anaphylaxis) of three drugs. **Materials and Methods:** This study is a multicentric, prospective, randomized, comparative study. This study was conducted on 150 patients of ST-elevation myocardial infarction admitted in the wards/ICCU- Intensive Coronary Care Unit, Department of Cardiology, Mahatma Gandhi Memorial Hospital and Rohini Superspeciality Hospital. They were selectively divided into three groups. Group A consisted of patients who received SK (50), Group B who received tenecteplase (50), and Group C who received reteplase (50). The study period was 6 months. The follow-up was done in all the patients during their inhospital stay. **Results:** Post thrombolysis, reteplase, tenecteplase, and SK led to mean ST-Segment reduction of 64.9 ± 19.77, 52.43 ± 34.57, and 46.97 ± 33.09, respectively. The comparison between the three drugs revealed a significant difference ($P = 0.0103$). **Conclusion:** This study concluded that reteplase is most efficacious in the resolution of ST-elevation and also safer than other thrombolytics used.

Keywords: Reteplase, ST-elevation myocardial infarction, streptokinase, tenecteplase, thrombolytics

Introduction

ST-elevation myocardial infarction (STEMI) is one of the challenging problems among acute coronary syndromes.[1] STEMI is a clinical syndrome characterized by typical symptoms of myocardial ischemia associated with persistent electrocardiographic ST-elevation and subsequent release of myocardial necrotic biomarkers. The Universal Definition of Myocardial Infarction defined by the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association (AHA)/World Heart Federation Task Force is defined as new ST-elevation at the point J in at least two contiguous leads of ≥1.5 mm (0.15 mV) in women or ≥2 mm (0.2 mV) in men in leads V2–V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads, is characteristic of diagnostic ST-elevation in the absence of left ventricular (LV) hypertrophy or left bundle branch block (LBBB). Coronary artery disease (CAD) is the leading cause of mortality worldwide, and over 7.4 million people died due to CAD in 2015.[3] Nearly three million STEMI cases are estimated to occur in India per year. Cardiovascular diseases are with the highest mortality rate in India accounting for about 21% of the deaths in 2010, with 10% of overall deaths occurring due to CAD.[1]

The ACC/AHA 2013 guidelines for the management of STEMI suggest fibrinolytic therapy when there is an anticipated delay in performing primary PCI within 120 min of first medical contact and lists available fibrinolytic agents (tenecteplase [TNK-tPA], reteplase [rPA], alteplase, and streptokinase [SK]).[4]

Access this article online

Quick Response Code:

Website: www.joicc.org

DOI: 10.4103/JICC.JICC_62_20

Address for correspondence: Dr. Sheshagiri Sharvana Bhava Bandaru, Department of Clinical Pharmacy and Pharm.D., Vaagdevi College of Pharmacy, Hanamkonda, Warangal - 506 001, Telangana, India.
E-mail: sharavanabhava6@gmail.com

How to cite this article: Neela B, Gunreddy VR, Chandupatla MR, Eggadi V, Bandaru SS. Safety and efficacy of streptokinase, tenecteplase, and reteplase in patients diagnosed with ST-elevation myocardial infarction: A comparative study. J Indian coll cardiol 2020;XX:XX-XX.

Submitted: 16-Aug-2020 **Accepted:** 21-Sep-2020 **Published:** ***

The hypothesis of our study was that reperfusion with new-generation fibrinolytics (TNK-tPA and rPA) will be effective than the SK. Besides this, the incidence of adverse events will be lesser with the new-generation thrombolytics.

Materials and Methods

Patients admitted to Mahatma Gandhi Memorial Hospital and Rohini Superspeciality Hospital, Warangal, with STEMI were enrolled for the study. The study was conducted according to widely accepted ethical principles guiding Human Research (Declaration of Helsinki). All the participants gave written informed consent, and the study has been approved (KIEC/KMC/NCT/NIS/2019/P36) by the Institutional Ethics Committee of Kakatiya Medical College, Warangal. It was a multicentric, prospective, randomized study.

This study was conducted on a total of 150 patients of STEMI admitted in the wards/ICCU, Department of Cardiology.

Inclusion criteria

Patients presented with chest pain within 12 h, those diagnosed with STEMI, and patients treated with thrombolytic agents were included in the study.

Exclusion criteria

Patients with any prior intracranial hemorrhage, known structural cerebral vascular lesions like arteriovenous malformation, severe uncontrolled hypertension (unresponsive to emergency therapy), known malignant intracranial neoplasm, ischemic stroke within 3 months except for acute ischemic stroke within 4.5 h, suspected aortic dissection, active bleeding or bleeding disorders, major trauma within 3 months, history of pacemaker implantation, intracranial or intraspinal surgery within 2 months, for SK- prior treatment within the previous 6 months, prior major surgery, peptic ulcer disease, anticoagulant therapy were excluded from this study.

To study the clinical outcomes of fibrinolysis, efficacy parameters such as mean ST-segment reduction, ST-elevation resolution of >50% on electrocardiogram (ECG), and chest pain relief (>50%) post thrombolysis were assessed. The complete resolution could be defined as the reduction in >70%, partial resolution as the reduction of 30%–70%, and no resolution as reduction of <30% after 180 min of post thrombolysis in ST. The pain was recorded with Numerical Pain Rating Scale (NPRS), an 11-point scale from 0 to 10 where 0 = no pain and 10 = the most intense pain imaginable, before and 90 min after fibrinolytic therapy. Safety parameters such as bleeding, hypotension, and anaphylaxis were also assessed with information from the patient case records.

The quantitative variables were expressed as mean ± standard deviation and compared within the groups using paired *t*-test/Wilcoxon test and between the groups by one-way ANOVA followed by Tukey's test. The qualitative variables were expressed as frequencies/percentages. $P < 0.05$ was considered statistically significant. GraphPad Prism version 8.3.1 was used for statistical analysis.

Results

A total of 150 patients of STEMI were included in the study. These were selectively divided into 3 groups of 50 each. Group A consisted of patients who received SK (50), Group B who received tenecteplase (50), and Group C who received reteplase (50).

The age distribution of the study population lies between 21 and 80 years. Majority of the patients in all the three groups are male [Table 1]. Among all the patients in three groups, 63 (42%) were smokers, 82 (54.66%) were alcoholics, 52 (34.6%) were both smokers and alcoholics, 64 (42.6%) had hypertension, 30 (20%) were diabetic patients, and 20 (13.33%) had both hypertension and diabetes mellitus.

All the patients ECG were assessed before and after thrombolytic therapy [Figure 1] for the calculation of mean values and to find the significant difference within groups and between the three drug groups, which yielded a significant value (P = 0.0103) [Table 2]. They were also evaluated for resolution of >50% ST-elevation and the results showed that rPA was more effective [Table 3].

All the patients were also evaluated for the relief in chest pain using NPRS score pre and post thrombolysis. A significant value was obtained within all three groups (P = 0.0001) and between the drug groups a P value (0.0283) was obtained, but in terms reduction in mean pain score and percent decrease, rPA was more effective [Table 4].

All the three groups were also evaluated for the safety of thrombolytic agents. The incidence of adverse effects in the rPA and TNK-tPA groups was equal (in about 4% of the patients), which reveals that they are superior to SK in terms of it [Table 5].

Discussion

Fibrinolytic therapy has become the mainstay of therapy

Table 1: Age and gender distribution of patients

	rPA, *n* (%)	TNK-tPA, *n* (%)	SK, *n* (%)
Age (years)			
21-40	3 (6)	12 (24)	1 (2)
41-60	28 (56)	27 (54)	26 (52)
61-80	19 (38)	11 (22)	23 (46)
Total	50 (100)	50 (100)	50 (100)
Mean±SD	56.36±11.46	50.34±12.10	60.11±11.20
Gender			
Male	38 (76)	41 (82)	34 (68)
Female	12 (24)	9 (18)	16 (32)
Total	50 (100)	50 (100)	50 (100)

TNK-tPA: Tenecteplase, rPA: Reteplase, SK: Streptokinase, SD: Standard deviation

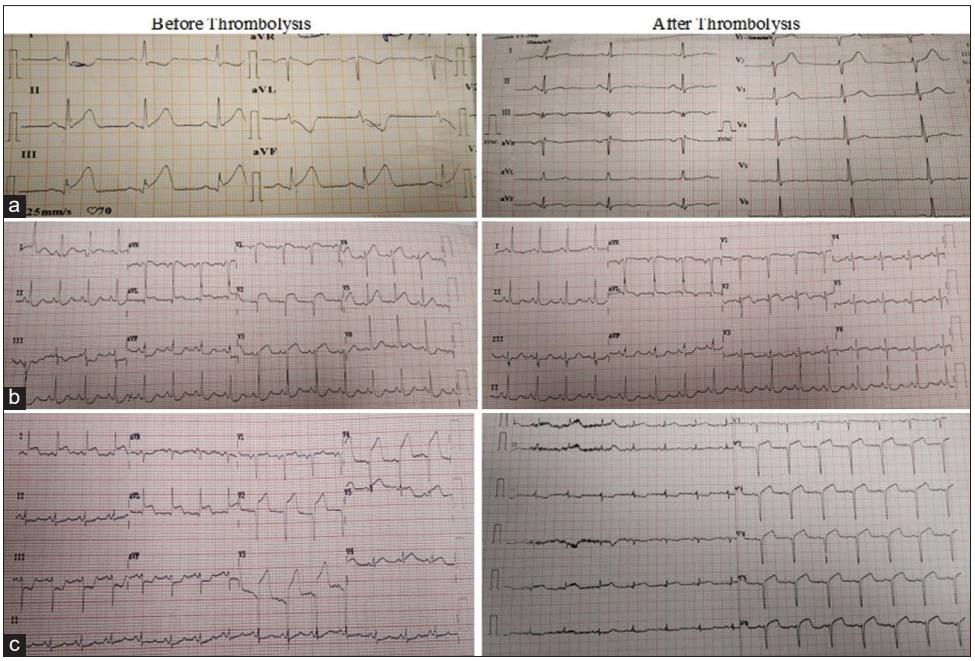

Figure 1: (a) Reteplase – inferior wall myocardial infarction. (b) Tenecteplase – anterolateral wall myocardial infarction. (c) Streptokinase – anterolateral wall myocardial infarction

Table 2: Efficacy of three thrombolytics (electrocardiogram)

Groups	ECG (ST segment)		Mean percentage decrease in ST-segment elevation	*P*
	Prethrombolysis	Postthrombolysis		
rPA	3.02±1.26	0.94±1.01	68.87±19.84	<0.0001****
TNK-tPA	3.28±1.77	1.56±1.16	52.43±34.46	<0.0001****
SK	2.98±1.57	1.58±1.05	46.97±33.12	<0.0001****

Ordinary one-way ANOVA, *P*: 0.0103* * P ≤ 0.05, ** P ≤ 0.01, **** P ≤ 0.0001

Tukey's multiple comparisons test

Groups	Adjusted *P*	Significant
rPA versus TNK-tPA	0.0967	No
rPA versus SK	0.0089**	Yes
TNK-tPA versus SK	0.6392	No

TNK-tPA: Tenecteplase, rPA: Reteplase, SK: Streptokinase, ECG: Electrocardiogram

Table 3: ST-segment resolution

Parameters	rPA (*n*=50), *n* (%)	TNK-tPA (*n*=50), *n* (%)	SK (*n*=50), *n* (%)
ST-segment resolution >50% after lysis	43 (86)	35 (70)	26 (52)
In terms of complete, partial, and no resolution			
Complete resolution (>70%)	28 (56)	12 (24)	11 (22)
Partial resolution (30%-70%)	16 (32)	28 (56)	22 (44)
No resolution (<30%)	6 (12)	10 (20)	17 (34)

TNK-tPA: Tenecteplase, rPA: Reteplase, SK: Streptokinase

for acute myocardial infarction. First-generation thrombolytics have clinical disadvantages such as low fibrin specificity, shorter half-life, and an enhanced risk of allergic reactions (especially for SK). The potential benefits have come from newer thrombolytic agents including rPA and TNK-tPA including high fibrin sensitivity, longer half-life, and improved plasminogen activator tolerance. However, these laboratory-mediated advantages may not translate into measurable and useful clinical results. Lanoteplase, a new thrombolytic drug, was withdrawn from development due to its increased risk of intracranial hemorrhage.[5,6]

Many findings in the last 10 years led to a reassessment of ST-elevation monitoring utility after STEMI. Schro¨der

Table 4: Efficacy of three thrombolytics (Numerical Pain Rating Scale score)

Groups	NPRS score		Mean percentage decrease in pain score	*P*
	Prethrombolysis	Postthrombolysis		
rPA	7.78±1.60	1.60±1.03	79.43±35.90	<0.0001****
TNK-tPA	8.10±1.23	1.92±1.10	76.29±10.49	<0.0001****
SK	8.10±1.11	2.08±1.08	74.32±2.35	<0.0001****

Ordinary one-way ANOVA, *P*: 0.0283 **P ≤ 0.05, **P ≤ 0.01, ****P ≤ 0.0001

Chest pain relief in terms of >50%		
rPA (*n*=50), *n* (%)	TNK-tPA (*n*=50), *n* (%)	SK (*n*=50), *n* (%)
50 (100)	49 (98)	47 (94)

NPRS: Numerical Pain Rating Scale, TNK-tPA: Tenecteplase, rPA: Reteplase, SK: Streptokinase

Table 5: Safety profile of three drugs

	rPA (*n*=50)	TNK-tPA (*n*=50)	SK (*n*=50)
Bleeding (%)	3 (6)	2 (4)	5 (10)
Hypotension (%)	1 (2)	2 (4)	3 (6)
Anaphylaxis (%)	0	0	1 (2)
Total (%)	4 (8)	4 (8)	9 (18)

TNK-tPA: Tenecteplase, rPA: Reteplase, SK: Streptokinase

et al. showed that ST-segment resolution can predict accurately the risk of death and congestive heart failure in patients treated with fibrinolytic therapy. Resolution of ST-elevation is now being used with increasing frequency in the determination of prognosis early after fibrinolytic therapy and direct comparison of different reperfusion regimens.[7,8]

In patients around the world with sudden and severe STEMI, fibrinolytic remedy with SK and tissue plasminogen activators inclusive of TNK-tPA, rPA, and alteplase has a profound effect and the ability of these agents to obtain fast and efficient coronary reperfusion as systemic intravenous bolus or infusion has without a doubt modified the therapeutic approach.[9,10] In a study done by Ranakishore *et al*., they concluded RTP (90%) = SK (90%) >TNK (86%) in terms of >50% resolution of ST-elevation and RTP (96.66) >SK (93.33) >TNK (83.33) in terms of >50% resolution of symptoms.[11] Their study results were not in concordance with our study which concluded rPA (86%, 100%) >TNK-tPA (70%, 98%) >SK (52%, 94%) in terms of both efficacy parameters, respectively. The study was consistent with their study in terms of safety. In the study done by Uneeba Syed, 130 patients were treated with SK and the mean reduction in ST-elevation was noted as 58.53 ± 26.01.[12] It was not concordant with our study which showed a mean reduction of 46.97 ± 33.09 in ST-elevation. In terms of NPRS score in a study conducted by Ramya *et al*.,[13] the mean score of pain was reduced tremendously after thrombolysis (SK) and those results were statistically significant ($P < 0.0001$) and were similar to our results obtained.

Bleeding is the main adverse effect of thrombolytics. In this research work, 4% of patients in the TNK-tPA group and 10% of patients in the SK group experienced bleeding. It was not consistent with a previous study done by Yazdi *et al*. In their study of 142 patients, 28.4% and 35.1% of patients treated with TNK-tPA and SK experienced bleeding, respectively.[14]

In this research work, the incidence of adverse events in the rPA group was 8%, and resolution of 50% ST-elevation and resolution of symptoms were reported in 86% and 100% of patients, respectively. These results were not consistent with the previous study done by Singh *et al*. In their study, 228 patients were treated with rPA. The incidence of adverse events was 5.3%, and resolution of 50% ST-elevation and resolution of chest pain were reported in 90.50% and 95.4% of patients, respectively.[15]

A postlicensure, observational, prescription event monitoring study of 2100 patients of STEMI was done by Iyengar *et al*. in 2009. In their study, 4.62% of TNK-tPA patients had experienced bleeding.[16] It was concordant with our study results, in which 4% of patients had bleeding. A multicentric, observational, prescription event monitoring study of 7668 patients of STEMI was done by Iyengar *et al*. in 2017. In their study, 93.2% of patients had chest pain resolution after pharmacological fibrinolysis with TNK-tPA,[17] but in our research work by a tiny fraction of 5%, 98% of patients had chest pain resolution.

A systemic review of randomized controlled trials comparing the clinical efficacy of newer (reteplase and tenecteplase) and older (alteplase and SK) thrombolytic agents was done by Dundar *et al*., and their study concluded that SK was associated with a higher incidence of allergic reactions, which also included anaphylaxis.[18] It is concordant with our study which also showed that a patient treated with SK had an anaphylactic reaction, but the other two groups did not report any.

Conclusion

Our results suggest that reperfusion therapy with fibrin-specific fibrinolytics (rPA and TNK-tPA) is the optimum treatment regimen for patients. SK seems to be less effective in terms of safety and efficacy. Research on reteplase must be encouraged on a regular basis and make it available in all the emergency setups. Establishment of safety and efficacy of rPA and other thrombolytic agents and their comparative evidence helps the clinicians to choose an appropriate agent on an individual basis.

More thrombolytic agents are needed to be designed, and more comparative shreds of evidence are to be established to reduce the morbidity and mortality of myocardial infarction patients. As a probable extension, two-dimensional echocardiography parameters such as ejection fraction and LV function can also be assessed. Patients' education on the disease and emergency condition, first-aid measures, and long-term follow-up after thrombolytic therapy may help the patient and researcher to work more effectively.

Limitations

Findings derived from this study might not be directly inferable to the treatment strategy of all patients because the study was conducted in a sample size of 50 in each drug group and the clinical effectiveness of the drugs in long-term period could not be established due to noncompliance of patients for further follow-up.

Acknowledgments

We express our gratitude to the Institutional Ethics Committee of Kakatiya Medical College, Warangal, for permitting us to conduct the study. We also thank all the patients who took part in this research work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Guha S, Sethi R, Ray S, Bahl VK, Shanmugasundaram S, Kerkar P, *et al*. Cardiological Society of India: Position statement for the management of ST elevation myocardial infarction in India. Indian Heart J 2017;69 Suppl 1:S63-S97.
2. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, *et al*. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
3. Keys A, Aravanis C, Blackburn HW, Van Buchem FS, Buzina R, Djordjević BD, *et al*. Epidemiological studies related to coronary heart disease: Characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl 1966;460:1-392.
4. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., Chung MK, de Lemos JA, *et al*. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-425.
5. Armstrong PW, Collen D. Fibrinolysis for acute myocardial infarction: Current status and new horizons for pharmacological reperfusion, part 1. Circulation 2001;103:2862-6.
6. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators; Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, *et al*. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. Lancet 1999;354:716-22.
7. Deshmukh A, Pandya J, Hilleman D, White M, Lanspa T, DelCore M, *et al*. Impact of obesity on long-term outcomes in patients with acute stemi treated with PCI. J Am Coll Cardiol. 2013; 61:E207.
8. Schröder R, Dissmann R, Brüggemann T, Wegscheider K, Linderer T, Tebbe U, *et al*. Extent of early ST segment elevation resolution: A simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994;24:384-91.
9. Llevadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. JAMA 2001;286:442-9.
10. Bhatt S, Dilip K, Pai KS. Evaluation of Potato tuber carboxypeptidase inhibitor with standard anti-thrombotic drugs in various thrombosis models. Int J Pharm Bio Sci 2010;1:1-9.
11. Ranakishore P, Vanitha R, Ramesh M, Kannan G, Thennarasu P. Safety and efficacy of streptokinase, reteplase and tenecteplase in patients with acute ST-elevated myocardial infarction in an intensive cardiac care unit of a tertiary care teaching hospital. Int J Pharm Bio Sci. 2014; 5:29-38.
12. Syed U. Reduction of ST segment elevation in diabetic patients With myocardial infarction after thrombolytic therapy. J Ayub Med Coll Abbottabad 2017;29:308-10.
13. Ramya NS, Narendra JB, Raghavulu V, Babu MS, Teja ND, Malini KH, *et al*. Assess the clinical efficacy of streptokinase in thrombolysed patients of acute ST segment elevation myocardial infarction. J Young Pharm 2018;10:330-3.
14. Yazdi AH, Khalilipur E, Zahedmehr A, Pouya SA, Pakrou M, Ghaznavi MA, *et al*. Fibrinolytic Therapy With Streptokinase vs Tenecteplase for Patients With ST-Elevation MI Not Amenable to Primary PCI. Iranian Heart Journal. 2017; 18:43-49.
15. Singh RK, Trailokya A, Naik MM. Post-reteplase evaluation of clinical safety & Efficacy in Indian patients (precise-in study). J Assoc Physicians India 2015;63:30, 32-5.
16. Iyengar SS, Nair T, Sathyamurthy I, Hiremath JS, Jadhav U, Kumbla D, *et al*. Efficacy and safety of tenecteplase in ST elevation myocardial infarction patients from the Elaxim Indian Registry. Indian Heart J 2009;61:480-1.
17. Iyengar SS, Nair T, Hiremath J, Dutta AL, Jadhav U, Katyal VK, *et al*. Pharmacological reperfusion therapy with tenecteplase in 7,668 Indian patients with st elevation myocardial infarction-A real world indian experience. J Assoc Physicians India 2017;65:43-7.
18. Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: A systematic review. QJM 2003;96:103-13.