



Safety and Efficacy of Third Generation Thrombolytic- Tenecteplase in Acute Myocardial Infarction

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Abstract

Background: Coronary heart disease is the major cause of mortality and morbidity across the world. The developed countries are seeing a decrease in cases however, the developing countries are incidence is occurring in the younger population. We in the current study aimed to study the efficacy and safety of third-generation single bolus thrombolytic Tenecteplase (TNK) in our setup in patients with acute STEMI. **Methods:** This cross-sectional study was conducted in the Department of General Medicine/ Cardiology, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Patients were reporting to PIMS hospital with chief complaints of chest pain or shortness of breath, diagnosed as STEMI by standard 12 lead ECG criteria. All patients were diagnosed with STEMI. **Results:** Clinically significant thrombolysis was seen in 98% of patients. Ventricular tachyarrhythmias were developed in 3(3%) patients. 2 patients survived after electrical cardioversion and 1 patient died due to recurrent ventricular tachycardia and ventricular fibrillation despite cardioversion after 2 hours of Tenecteplase injection. One patient who was admitted in Killip class IV died within one hour of Tenecteplase bolus injection due to refractory hypotension and cardiogenic shock. **Conclusion:** Tenecteplase is the safest drug in our setup with the least rate of complications. The efficacy of the drug is still maintained even if it is given after a 6-hours' time window. This makes Tenecteplase a choice for pre-hospital thrombolysis. The higher patency rates and least rates of re-infarction are due to the efficacy of the drug in achieving successful thrombolysis and continuous infusion of heparin till taken up for angiography.

Keywords: STEMI (ST-Elevation Myocardial Infarction), Tenecteplase, Acute Myocardial infarction, Thrombolysis

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Introduction

Coronary artery disease (CAD) is a major cause of mortality and morbidity all over the world. There has been a 4-fold rise in coronary heart disease (CHD) prevalence in India during the past 40 years. Recent estimates from epidemiologic studies from various parts of our country indicate a prevalence of CHD to be between 7%- 13% in urban and 2%-7% in rural

populations. [1-5] The projected figures for the disability-adjusted life years lost due to coronary heart disease for the year 2020 would be 14.4 million and 7.7 million in men and women respectively as per the report of The Global Burden of Diseases. [6] According to the statistics of the Ministry of Health and Family Welfare, Government of India, our country has the highest burden of Acute Coronary Syndrome (ACS) patients in the world. [7] The most

complete data about contemporary trends in ST-elevation myocardial infarction (STEMI) patients come from CREATE, a large clinical registry of acute coronary syndrome patients from 89 large hospitals in 10 regions and cities across India. [8] Among the more than 20 000 patients enrolled in CREATE, over 60% had STEMI, a proportion that is substantially higher than in North American and European registries. Moreover, Indians are more likely to develop CAD at younger ages during an individual's working years, and as a result, there is an extremely high loss of potentially productive years of life in India. The increasing burden of CHD in India can be explained by the alarming rise in the prevalence of coronary risk factors like diabetes mellitus, hypertension, dyslipidemia, smoking, central obesity, and lack of physical activity. Rapid urbanization and lifestyle changes that occurred over the past two decades have led to the growing burden of coronary risk factors in India. The conventional risk factors accounted for most of the CHD burden in India as per the large INTER HEART study. [9] The mainstay of treatment for acute STEMI is timely reperfusion, which can be accomplished through PCI or thrombolysis. Timely reperfusion can limit the amount of myocardial damage as said by the adage time is muscle. It can also prevent the future development of complications like cardiac dysfunction and morbidities and mortalities related to it. The first-generation thrombolytic streptokinase was used successfully for many years and is still in usage in developing countries like India. It is a non-fibrin-specific agent, and it was less effective in opening the infarct-related artery. But later with the introduction of fibrin-specific agents like Tenecteplase complications were reduced and the success of thrombolysis was increased. Restenosis of the infarct-related artery is the main problem with fibrinolytic, whereas primary Percutaneous Coronary Intervention (PCI) achieves immediate and sustained patency of the infarct-related artery. Multiple studies have shown the superiority of primary PCI both in terms of efficacy and mortality.

Materials and Methods

This cross-sectional study was conducted in the Department of General Medicine/ Cardiology,

Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Institutional Ethical Committee approval was obtained for the study. Written consent was obtained from all the participants of the study or their relatives after explaining the nature of the study with its complications were explained clearly.

Inclusion criteria

1. Patients between age groups 20-70 years
2. Diagnosed as having acute STEMI based on clinical symptoms and standard 12 lead ECG criteria.
3. Patients presenting within 12 hours
4. With or without hypertension, diabetes mellitus, and dyslipidemia.

Exclusion criteria

1. Age <20 years or > 70 years
2. Prior history of CAD
3. Prior history of stroke- Ischemic or hemorrhagic
4. Patients in hypertensive urgency or emergency
5. Delayed presentation > 12 hours

Sample Size calculation

Based on the inclusion and exclusion and sample size calculation using formula $n = Z^2 pq / E^2$ if 5% of the population is affected and the approximate population size is 500,000 then the sample size was $n=73$ we have included $n=100$ cases. Patients were reporting to PIMS hospital with chief complaints of chest pain or shortness of breath, diagnosed as STEMI by standard 12 lead ECG criteria. All patients diagnosed as STEMI initially received dispersible Aspirin 325 mg, Clopidogrel 300 mg, and Atorvastatin 40 mg. After ruling out contraindications, all patients received a weight-adjusted dose of Tenecteplase (0.53 mg/kg) as a single intravenous bolus. Two-dimensional Echocardiography was done to assess cardiac function. All the patients were closely monitored for any complications. After successful thrombolysis, all patients received heparin either as continuous intravenous infusion or subcutaneous route. All the patients with successful thrombolysis were taken up to angiography between 2 to 5 days. Further treatment was advised based on angiographic results, i.e., either PTCA or CABG.

Results

A total of n=100 patients who presented to our hospital with acute STEMI were included in the study. Younger patients below 20 years and older patients above 70 years were excluded from the study. There were n=84, males, and n=16 females with a mean age of 50.39 years. SD=16.97 years. The average age of presentation in males is 50.13 years (SD=3.53 years) and that of females is 51.57 years (SD=2.12 years). This shows that the first attack of STEMI in males is little age earlier than in females.

Table 1: Age and Sex Distribution of STEMI Patients

	Males	Females	Total sample
Number	84	16	100
Maximum Age (Years)	67	65	67
Minimum Age (Years)	25	42	25
Average Age (Years)	50.13	51.57	50.39
Standard Deviation (Years)	3.53	2.12	16.97

Hypertension is the commonest risk factor in the study followed by smoking, diabetes, and dyslipidemia in the order. Hypertension accounted for 48 percent which is the most common risk factor in the overall population of the study. Hypertension is also the most common risk factor in males (48.8%) and the female subgroup (43.75%) Smoking is the second most common risk factor for STEMI in the study which accounted for 37% The next common risk factors include diabetes mellitus and dyslipidemia which constitute 29% and 20% respectively.

The window period is defined as the time difference between the onset of symptoms to the first medical contact. Only 11% of our patients presented within 3 hours of the onset of symptoms.

72% of patients presented between 3 to 6 hours. 17% of patients presented to the hospital after 6 hours. The average time of presentation to the hospital after the onset of symptoms is 5.27 hours. All the patients diagnosed with STEMI were included in the study. None of the patients had a misdiagnosis of acute STEMI. Anterior

wall infarction was seen in 61% of patients followed by inferior wall myocardial infarction in (20%) patients. Inferior posterior wall myocardial infarction was seen in 13% of patient's Inferior wall with right ventricular myocardial infarction was seen in 5% of patients. An inferior wall with lateral wall involvement is seen in 1 patient.

Table 2: Baseline cardiac function at admission

LV ejection Fraction	Cardiac function	Percentage of patients
>60%	Good LV function	22
50-59%	Fair LV function	8
45-49%	Mild LV dysfunction	48
35-44%	Moderate LV Dysfunction	18
<35%	Severe LV dysfunction	4

About 25% of patients admitted were in Killip class I. 40% of patients were in class II. 25% of patients were in class III and 10% of patients were in class IV. All patients diagnosed with STEMI received adjuvant treatment like aspirin and clopidogrel. 98% of patients received heparin (either regular unfractionated heparin or low molecular weight heparin). 38% of patients received beta-blockers. Patients who received were of having mild to moderate dysfunction. Patients with severe cardiac dysfunction and patients with cardiogenic shock did not receive beta-blockers. 42% of patients received nitrates. Patients with severe chest pain and with anterior wall STEMI received nitrates. Patients with inferior wall STEMI right ventricular STEMI did not receive nitrates. None of the patients received GP IIb/IIIa Inhibitors.

Table 3: % Receiving Adjuvant Treatment

Drug received	Percentage of patients
Aspirin	100
Clopidogrel	100
Heparin	98
Beta-blockers	38
Nitrates	42
GP IIB/IIIA Inhibitors	0

All the patients were thrombolysis with a weight-adjusted dose of Tenecteplase (0.53mg/kg) after ruling out all contraindications for Tenecteplase. The average duration for clinically successful thrombolysis in our study was around 90 minutes. Clinically

significant thrombolysis was seen in 98% of patients. Ventricular tachyarrhythmias were developed in 3(3%) patients. 2 patients survived after electrical cardioversion and 1 patient died due to recurrent ventricular tachycardia and ventricular fibrillation despite cardioversion after 2 hours of Tenecteplase injection. One patient who was admitted in Killip class IV died within one hour of tenecteplase bolus injection due to refractory hypotension and cardiogenic shock. Reperfusion arrhythmias like accelerated idioventricular rhythm were seen in 7% of patients. (5% patients with IWMI and 2% patients with AWTMI. None of the patients developed central nervous system bleed. One patient developed a major access site complication. Reinfarction developed in 4% of patients.

Table 4- Safety Parameters of Tenecteplase

Parameter	% of patients
Clinically significant Thrombolysis	98
Intracerebral hemorrhage	0
Major access site bleeding	1
Ventricular arrhythmias	3
Reinfarction	4
Cardiac failure/cardiogenic Shock	1
Death	2

Table 5- Angiographic profile of stemi patients

	LAD	RCA	LCX
Isolated involvement	54 (55.1%)	12 (12.24%)	8 (8.16%)
As a part of double vessel disease	9(9.18%)	9(9.18%)	7(7.14%)
As a part of triple vessel disease	11 (11.22%)	11 (11.22%)	11 (11.22%)
Total	74 (75.5%)	32 (32.65%)	26 (26.53%)

Recanalized vessels or insignificant stenosis, (i.e., stenosis <50%) was seen in 24 patients. (22.44%) Of the 24 patients 18 patients had recanalized LAD, 2 patients had recanalized RCA and 2 patients had recanalized LCX artery. One patient had recanalization of both LAD and LCX, one patient had recanalization of both RCA and LCX. Single vessel disease (i.e., involvement of single artery with >50% stenosis) was seen in 54 patients. (57.10%) Of these 54 patients, 35 patients had isolated LAD

disease, 12 patients had isolated RCA disease, 7 patients had isolated LCX disease. Double vessel disease (involvement of two arteries with >50% stenosis) was seen in 9 patients (9.18%) Among the 9 patients, LAD with RCA involvement was seen in 4 patients, LAD with LCX involvement was seen in 2 patients, RCA with LCX involvement was seen in 3 patients Triple vessel disease was seen in 11 patients (11.22%)

Table 6: Outcome of stemi patients

Outcome	Number of Patients	Percentage
Insignificant Disease/ medical Management	24	24%
Ptca/stenting	61	61%
Cabg	13	13%
Mortality	2	2%
Total	100	100%

The insignificant disease was seen in 24 patients and was treated medically. PTCA/stenting was done in 61 patients. CABG was done in 13 patients. There were no procedural complications during PTCA or CABG the Overall mortality was 2 percent (table 6).

Discussion

Our study proves the safety and efficacy of pharmacoinvasive strategy as a means of treating acute STEMI in places where cath lab facilities are scarce. N=100 patients were included in our study the mean age of the population in this study was 50.39 years. According to the INTERHEART study [9], the median age of first heart attack in Indians is 53 years whereas that in Western Europe, China, and Hong Kong is 63 years, with more men affected than women. [1] Asian Indians develop heart attacks 6-10 years earlier than other Populations. In this study, we found the various risk factors as hypertension in 48%, Diabetes mellitus in 29% of cases. Smoking was an etiological factor in 37% of cases and 20% were cases of dyslipidemia. In a similar study Raman K et al., [10] conducted a field survey in Kerala's rural population in 1993. He found that the prevalence of risk factors like hypertension, diabetes mellitus, and smoking was 18.8%,4%, and 21.9% respectively. Chadha et al., [11] in their study prevalence of risk factors like hypertension, diabetes mellitus, smoking, and

dyslipidemia was 10.6%, 1.55%, 18.1%, and 43.7% respectively. Singh et al.,^[12] found 23.4%, 4.5%, 19.7%, and 22% for hypertension, diabetes mellitus, smoking, and dyslipidemia respectively. The average time of presentation to the hospital after the onset of symptoms in this study was 5.27 hours the duration between 3 – 6 hours is called the golden period for thrombolysis. S Iyenger et al.,^[13] showed the range of presentation in cases was < 3 hours for 64.42% cases, followed by 3 – 6 hours in 29% cases and > 6 hours in 6.57% cases. The delayed presentation of several cases in this study was due to lack of proper education, lack of awareness and time is taken for shifting the patient from a rural setting to a hospital. Anterior wall infarction is the most common site of infarct in the present study which accounted for 61 percent of cases. 39% cases had non-anterior wall myocardial infarction which includes 20% cases of isolated inferior wall infarction, 13% cases of inferior with posterior wall infarction, 5% cases of the inferior wall with right ventricular infarct, and 1% cases with inferior and lateral wall infarct. S Sameer et al.,^[14] in their study found Anterior MI in 39.8% cases followed by inferior MI in 33.7% cases, lateral MI was in 14.5% and Inferior and right ventricular MI was in 12% cases. In the present study, 100% of patients of the study group received aspirin, 100% patients received clopidogrel, 98% patients received heparin, 38% patients received beta-blockers, 42% patients received nitrates and none of the patients received GP IIb/IIIa inhibitors. The overall success rate of Tenecteplase in this study was 98% The overall rate of clinically successful thrombolysis in S Iyenger et al.,^[13] study was 86.71% and 98% in the present study which are comparable (p=0.4008). In the present study clinically, significant thrombolysis was seen in 100% males and 87.50% females which are comparable, and the difference was insignificant (p=0.7366). S Iyenger et al.,^[13] study found clinically significant thrombolysis was found in 95.57% males compared to 100% males in the present study. In females, the rate of clinically significant thrombolysis was 94.69% in the present study.

Limitations of the study

This is a cross-sectional study with very small sample size and the study group is not

randomized. We excluded older people greater than 70 years of age in our study. Therefore, bleeding complications which are almost negligible in our study cannot be generalized to the total population.

Conclusion

Tenecteplase is the safest drug in our setup with the least rate of complications. The efficacy of the drug is still maintained even if it is given after a 6-hours' time window. This makes Tenecteplase a choice for pre-hospital thrombolysis. The higher patency rates and least rates of re-infarction are due to the efficacy of the drug in achieving successful thrombolysis and continuous infusion of heparin till taken up for angiography. The mortality rate is higher in females compared to males. About one-fourth of the patients had the insignificant disease after thrombolysis. If these patients would have been taken up for primary PCI, these patients would have been ended up instituting stents as a part of primary PCI and angioplasty. Therefore, this strategy had avoided unnecessary stents in these patients and further complications related to stents like stent thromboses.

Conflict of Interest: None

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Ethical Permission: Obtained

References

1. Mohan V, Deepa R, Rani SS, et al. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India. *J Am Coll Cardiol.* 2001; 38:682e687.
2. Gupta R, Gupta VP, Sarna M, et al. Prevalence of coronary heart disease and risk factors in an urban Indian population: Jaipur Heart Watch-2. *Indian Heart J.* 2002; 54:59e66.
3. Kamili MA, Dar IH, Ali G, et al. Prevalence of coronary heart disease in Kashmiris. *Indian Heart J.* 2007; 61:44e49.
4. Gupta AK, Bharadwaj A, Ashotra S, et al. Feasibility and training of multipurpose workers in detection, prevention and control of coronary artery disease in apple-belt of Shimla hills. *South Asian J Prev Cardiol.* 2002; 6:17e22.

5. Kumar R, Singh MC, Ahlawat SK, et al. Urbanization and coronary heart disease: a study of urban-rural differences in northern India. *Indian Heart J.* 2006; 58:126e130.
6. Ezzati M, Lopez AD, Rodgers A, et al. Comparative Quantification of Health Risks. Global and Regional Burden of Disease Attributable to Major Risk Factors. Geneva: World Health Organization; 2004.
7. National Commission on Macroeconomics and Health. The burden of Disease in India. Delhi, India: Ministry of Health and Family Welfare, Government of India. [https://www.who.int/macrohealth/action/NCMH_Burden%20of%20disease_\(29%20Sep%202005\).pdf](https://www.who.int/macrohealth/action/NCMH_Burden%20of%20disease_(29%20Sep%202005).pdf) [Accessed on 07/08/2021]
8. Xavier D, Pais P, Devereaux PJ, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet.* 2008; 371:1435–1442
9. Yusuf S, Hawken S, Ounpuu S, et al. The INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364:937e952.
10. Raman Kutty V., Balakrishnan K.G., Jayasree A.K., Thomas Jessy. Prevalence of coronary heart disease in the rural population of Thiruvananthapuram district, Kerala, India. *Int J Cardiol.* 1993; 39:59–70.
11. Chadha S.L., Gopinath N., Shekhawat S. Urban-rural differences in the prevalence of coronary heart disease and its risk factors in Delhi. *Bull World Health Organ.* 1997;75(1):31–38.
12. Singh R.B., Sharma J.P., Rastogi V. Prevalence of coronary artery disease and coronary risk factors in rural and urban populations of north India. *Eur Heart J.* 1997; 18:1728–35.
13. Iyengar Shamanna, Nair Tiny, Hiremath, J.S. Jadhav, Udhav Katyal, V.K. Kumbha, D et al., Pharmacologic Reperfusion Therapy with Indigenous Tenecteplase in 15,222 patients with ST-Elevation Myocardial Infarction – The Indian Registry. *Indian heart journal* 2013; 65. 436-441.
14. Sameer Saleem, A Khan, I Shafiq. Post thrombolytic resolution of ST elevation in STEMI patients. *Pak J Med Sci* 2016; 32(1): 201–205.