International Journal of Medical and Health Research
ISSN: 2454-9142, Impact Factor: (RJIF 5.54)
www.medicalsjournals.com
Volume 2; Issue 4; April 2016; Page No. 22-26

A study on role of tenecteplase in ST-segment elevation myocardial infarction

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Abstract
Aim: To study the role of tenecteplase in ST-segment elevation myocardial infarction.
Study Design: It is an observational study.
Study Group: Study group consisted of 50 patients who were diagnosed to have ST-segment elevation myocardial infarction in emergency department of Osmania general hospital.
Number of Patients: 50.
Period of The Study: 6 months, from December 2014 to May, 2015.
Inclusion Criteria: All those who were diagnosed to have ST-segment elevation myocardial infarction and present within the window period for thrombolysis and without any contraindications to thrombolytic therapy
Exclusion Criteria: All those who have contraindications for thrombolytic therapy.
Investigations: Electrocardiogram, serum levels of cardiac enzymes.

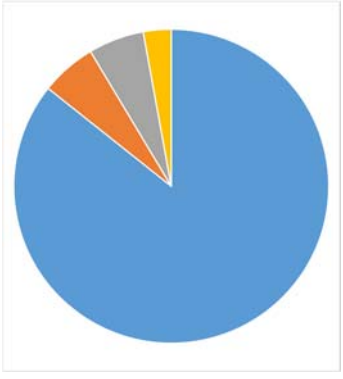
Keywords: Tenecteplase, elevation myocardial, Electrocardiogram.

Introduction

TNKase is a genetically engineered variant of the alteplase molecule. Three different mutations result in an increase of the plasma half-life, of the resistance to plasminogen-activator inhibitor 1 and of the thrombolytic potency against platelet-rich thrombi. Among available agents in clinical practice, TNKase is the most fibrin-specific molecule and can be delivered as a single bolus intravenous injection. Several large-scale clinical trials have enrolled more than 27,000 patients with acute myocardial infarction, making the use of this drug truly evidence-based. TNKase is equivalent to front-loaded alteplase in terms of mortality and is the only bolus thrombolytic drug for which this equivalence has been formally demonstrated. TNKase appears more potent than alteplase when symptoms duration lasts more than 4 hours. Also, TNKase significantly reduces the rate of major bleeds and the need for blood transfusions. The efficacy of TNKase may be further improved by enoxaparin substitution for unfractionated heparin, provided that enoxaparin dose adjustment is made for patients more than 75 years old. Hitherto, the small available randomized studies and international clinical registries suggest that pre-hospital TNKase is as effective as primary angioplasty, thus laying the foundations for a new fibrinolytic, TNKase-based strategy as the backbone of reperfusion in acute myocardial infarction.

Results

1. In our study we had 14 female patients and 36 male patients who presented to the emergency department of Osmania general hospital and were diagnosed to have ST-segment elevation myocardial infarction and presented within the window period. They didn't have any contraindications for thrombolysis and informed consent has been taken. All of them were thrombolysed with intravenous bolus dose of tenecteplase .53mg/kg body weight and successful thrombolysis was observed with post tenecteplase (after 90 minutes of tenecteplase administration) electrocardiogram recordings.
2. Successful thrombolysis was observed in 32 male patients, and 13 female patients.
3. 2 patients succumbed inspite of thrombolysis. Both the patients were in killips class 4, at the time of admission.
4. 2 patient with complete heart block following IWMI was taken up for TPI, following TNKase
5. 1 patient has intracranial bleeding following administration of tenecteplase.



- Blue-successful thrombolysis-90%(45 patients)
- Orange-deaths-4%(2 patients)
- Grey-TPI-4%(2 patients)

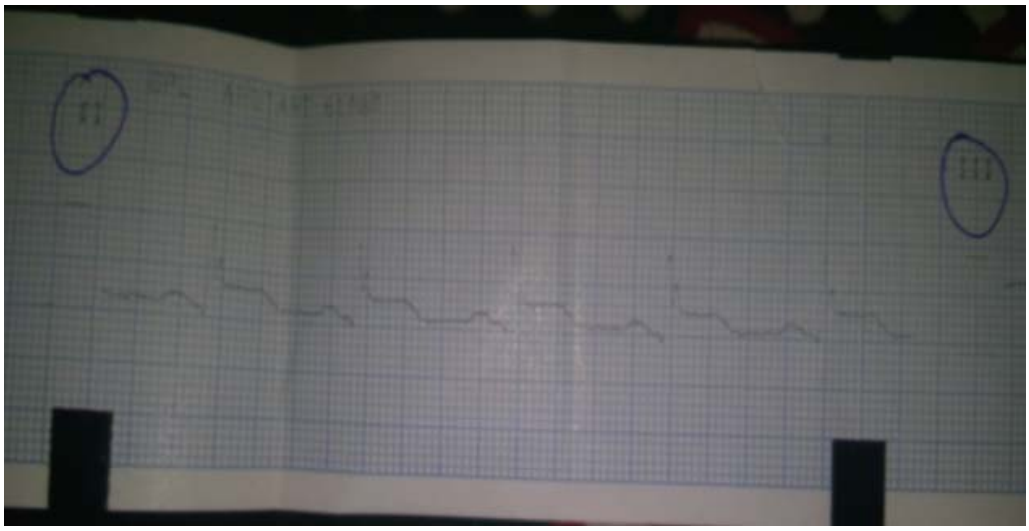


Fig 1: Pre-Tenecteplase

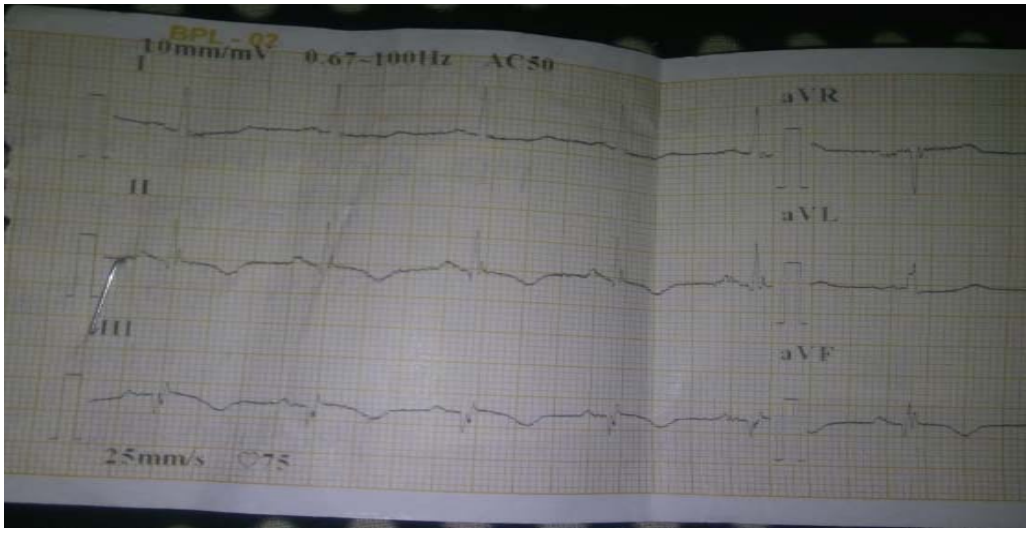


Fig 2: Post-Tenecteplase

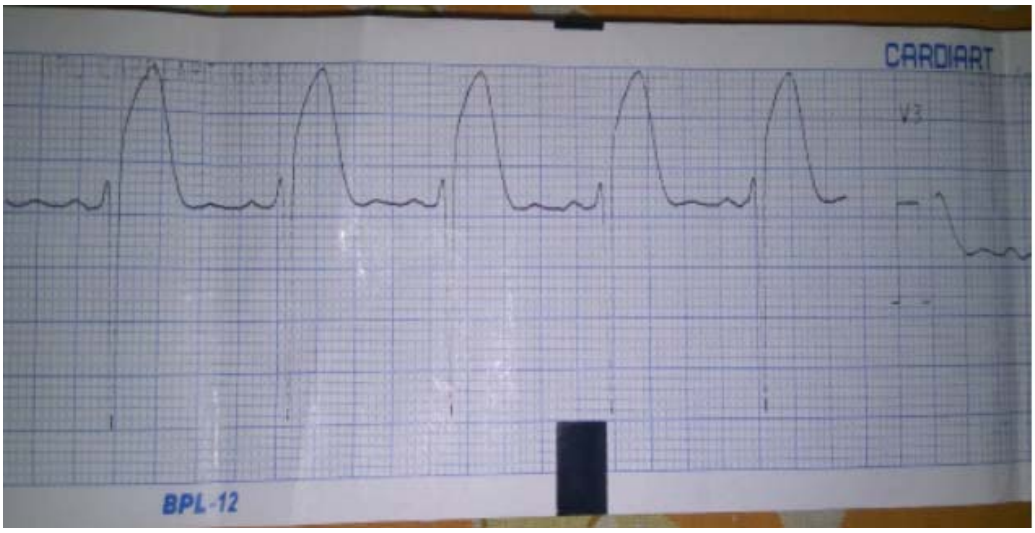


Fig 3: Pre-Tenecteplase

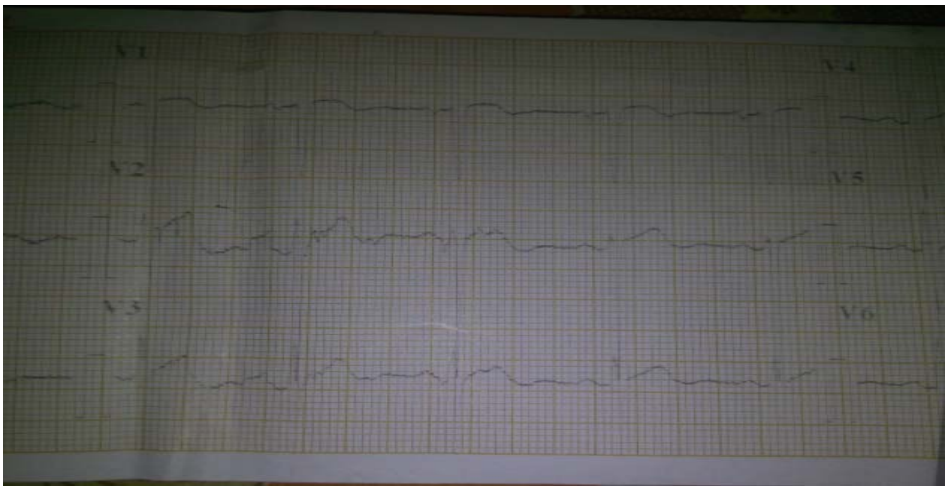


Fig 3: Post-Tenecteplase

Discussion

Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese hamster ovary cells). Tenecteplase is a 527 amino acid glycoprotein developed by introducing the following modifications to the complementary DNA (cDNA) for natural human tPA: a substitution of threonine 103 with asparagine, and a substitution of asparagine 117 with glutamine, both within the kringle 1 domain, and a tetra-alanine substitution at amino acids 296–299 in the protease domain.

Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.

4 The molecule is expressed in Chinese hamster ovary cells with carbohydrate side chains linked to the glycosylation sites of the polypeptide. At the N domain, the substitution was made to increase the fibrin specificity by focusing the enzymatic activity at the clot rather than the periphery thereby minimizing the induction of a systemic fibrinolytic state. In fact, levels of fibrinogen, fibrin degradation products, and other coagulation factors are fairly stable following TNK-tPA administration. TNK-tPA is 14 times more fibrin specific than standard tPA. 10 The blood clot has a fibrin portion that can be dissolved by PAs, exposing the clot-bound thrombin and, in turn, stimulates platelet aggregation. The plasminogen activator inhibitor-1 (PAI-1) is an enzyme attached to the surface of platelets that interacts with thrombolytics to inhibit their activity. TNK-tPA is 80–fold more resistant to inhibition from PAI- 1 than tPA. Liver metabolism is the major clearance mechanism of TNK-tPA. In an animal model of acute arterial occlusion, a bolus of TNK-tPA was found to produce a 6 to 12-fold rapid recanalization and a greater degree of clot lysis on a μg.kg-1 basis, compared with a front-loaded tPA regimen. TNK-tPA is compatible for combination with a broad range of other medications, such as glycoprotein (GP) IIb/IIIa and low-molecular-weight heparin, while rPA and tPA may precipitate with the administration of heparin, a drug commonly used in treating acute MI.

Clinical Trials Relevant To The Development Of Tenecteplase: Timi-10a

The Thrombolysis in Myocardial Infarction (TIMI)-10A Trial was a phase I, dose-ranging, pilot trial designed to evaluate the pharmacokinetics, safety and efficacy of the TNK-tPA in humans. Furthermore, it assessed the effects of increasing doses of TNK-tPA on the coagulation parameters and evaluated efficacy of using TIMI III flow and TIMI frame count. The study enrolled 113 patients with STEMI presenting within 12 hours of symptom onset who had no contraindications for thrombolysis. To establish the pharmacokinetic profile of the drug, the researchers used a small dose-escalation system, ranging from 5 to 50-mg bolus dose over 5 to 10 seconds. The results demonstrated a plasma clearance ranged from 125±25 to 216±98 mL/min and a prolonged half-life ranged from 11±5 to 20±6 minutes, allowing the administration of the drug as a single bolus. The fact that this thrombolytic agent can be administered in a bolus brings clear benefits. In addition to the speed and ease of use, the potential for errors is reduced.

This is an important consideration as some studies have reported incorrect dosing in up to 5% to 12% of the time, when using fibrinolytic therapy in the urgent setting of an acute STEMI. 21 Furthermore, mortality is increased in patients receiving incorrect doses of other thrombolytics, such as SK and tPA, which require IV infusion based on weight. The incorrect dosing may also be associated with increased ICH

There are additional pharmacokinetic considerations too - the consumption of α2-antiplasmin, fluid-phase inhibitor of plasmin, and a consequent increase in plasmin/α2-antiplasmin complexes, vary depending on the dose of TNK-tPA. There was a constant reduction on average at all dose levels in fibrinogen and plasminogen, 3% and 13% respectively. Results can be compared from those obtained with front-loaded tPA, which produce a decrease of 50% in fibrinogen and of 60% in plasminogen at 3 hours. Despite this, TNK-tPA is more fibrin specific than tPA. 12 The "plasminogen steal" phenomenon is produced by very low systemic levels of plasminogen leading to its diffusion out from the thrombus, depleting the substrate and decreasing the amount of plasmin generated on the clot surface, therefore decreasing clot lysis. In the case of double-bolus tPA, a lower rate of TIMI III flow and IRA patency is

observed. Because the double-bolus regimen can be associated with depletion of systemic plasminogen, a hypothesis states that plasminogen steal may reduce the efficacy of a more aggressive regimen. As such, the fibrin specificity of TNK-tPA should permit rapid plasminogen activation in the clot to proceed, even when given as a single bolus. 12 More than half of the patients (57-64%) experienced TIMI III flow at 90-minutes when treated with the 30 to 50-mg doses. Truly normal flow (TIMI frame count 27) was achieved by 45% of patients treated with higher doses of TNK-tPA, whereas only 27% of patients treated with tPA in the TIMI 4 trial achieved truly normal flow by 90-minutes (P<0.01).

Timi 10b Trial
TNK-tPA, given as a single 40-mg bolus, achieved rates of TIMI grade 3 flow similar to those of the 90-minute bolus and infusion of tPA. Weight-adjusting TNK-tPA appears to be important in achieving optimal reperfusion

Assent-1 Trial
Showed the efficacy and safety of low dose tenecteplase (40mg) in myocardial infarction.

Assent-2 Trial
Showed that tenecteplase had lower incidence of bleeding compared to other thrombolytics like t-PA.

Assent-3 Trial
This study showed the efficacy of combination of tenecteplase with low molecular weight heparin in treatment of acute myocardial infarction. However this combination was associated with increased risk of major bleeding.
All the above cited trials showed efficacy and safety of tenecteplase in acute myocardial infarction.
However our study showed better efficiency of tenecteplase in thrombolysis compared to oyher studies.

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