Thrombolysis with Reteplase in the Management of ST-Elevation in Myocardial Infarction and Evaluation of Patients in a Primary Care Setup (TRIME Study)

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Abstract

Thrombolytic therapy for the management of ST-elevation myocardial infarction (STEMI) is upgraded with the development of newer thrombolytics. Streptokinase was discovered decades back followed by alteplase, reteplase and tenecteplase. For patients with STEMI, reported within 12 hours of symptom onset and with persistent ST-segment elevation; early mechanical (PCI) or pharmacological (thrombolysis) reperfusion should be performed as early as possible[1]. Thrombolysis is an important reperfusion strategy, particularly in those settings where primary PCI cannot be offered to STEMI patients within the recommended timelines. Efficacy of a thrombolytic therapy depends upon factors like choice of thrombolytic agent, time of clinical presentation and adjunctive therapy[2]. Reperfusion rates with thrombolytics can be improved with adjunctive therapy such as direct antithrombin agents, low-molecular-weight heparin, or glycoprotein IIb/IIIa receptor antagonists.

Reteplase (r-PA) is a deletion mutant of wild-type tissue plasminogen activator. Its relatively longer half life allows administration as a bolus injection. Reteplase is administered as two bolus injections of 10 units each. Each bolus is administered over 2 minutes. The second bolus is given 30 minutes after the first bolus injection. The value of anticoagulants and anti-platelet drugs during and following administration of Reteplase has not been studied and heparin has been administered concomitantly in most of the patients. Aspirin has been given either during and/or following heparin treatment.

The current review evaluates the safety and efficacy of reteplase in acute ST elevation in myocardial infarction (STEMI). In all 67 patient data is being evaluated and the results of the study are discussed as per varied factors.

Keywords

Left bundle branch block (LBBB), ST elevation myocardial infarction (STEMI), reteplase (r-PA), acute myocardial infarction (AMI), tissue plasminogen activator (tPA), percutaneous coronary intervention (PCI), streptokinase (SK)

Introduction

The primary goal of thrombolytic therapy is to produce rapid, complete, and sustained restoration of infarct artery blood flow. Thrombolytic therapy has been available for the past 5 decades, though the modern era of thrombolysis began in the early 1990s. Thrombolytic therapy also offers

a potentially less invasive option for the treatment of patients with peripheral arterial and venous occlusions. Although it appears practically attractive, thrombolytic therapy has been criticized on the basis of a reocclusion rates and cost dynamics. Some of the criticisms were based on a misunderstanding of therapeutic expectations. Experience has demonstrated that unmasked lesions were frequently neglected and it is crucial that the patient should be followed for the suspected lesion that caused the occlusion.

The genesis of tissue plasminogen activator (tPA) occured in the mid 1980s for acute coronary artery occlusion, where a naturally occurring fibrinolytic agent was produced. Natural tPA is a single-chain (527 amino acid) serine protease, and in contrast to most serine proteases (e.g., urokinase), the single-chain form has significant activity. tPA has potential benefits over other thrombolytic agents. For one, the agent exhibits significant fibrin specificity; in plasma, the agent is associated with little plasminogen activation. At the site of the thrombus, however, the binding of tPA and plasminogen to the fibrin surface induces a conformational change in both molecules, greatly facilitating the conversion of plasminogen to plasmin and dissolution of the clot. tPA also manifests the property of fibrin affinity, that is, it binds strongly to fibrin.

Reteplase is a non-glycosylated deletion mutant of tissue plasminogen activator, containing the kringle 2 and the protease domains of human tissue plasminogen activator. Reteplase contains 355 of the 527 amino acids of native tissue plasminogen activator (amino acids 1-3 and 176-527). Reteplase is produced by recombinant DNA technology with *E. coli*. Reteplase was developed with the goal of avoiding the necessity of a continuous intravenous infusion, thereby simplifying ease of administration[3].

Reteplase catalyzes the cleavage of endogenous plasminogen to generate plasmin. This plasminogenolysis takes place in the presence of fibrin. Plasmin in turn degrades fibrin, which is the main component of the matrix of thrombi, thereby exerting its thrombolytic action. The low fibrin affinity of reteplase was hypothesized to reduce the incidence of distant bleeding complications in a manner similar to that of SK over rPA in the GUSTO trial. In fact, several properties of reteplase may account for a decreased risk of hemorrhage, including poor lysis of older, platelet-rich clots. Reteplase has been shown to have no antigenic activity; antibodies to reteplase have not been observed in

any of 2400 patients tested for antibody formation[4]. This property has a significant advantage over streptokinase and its derivatives.

The clinical efficacy and safety profile of reteplase have been studied in three large, controlled clinical trials in patients with AMI[5-7].

The RAPID 1 study was a dose-ranging study designed to evaluate three dosage regimens of reteplase (15 MU single bolus, 10MU+5MU double bolus, and 10MU+10MU double bolus) vs standard dose alteplase (100 mg infused over 3 h. The reteplase double-bolus 10MU+10MU dosage regimen was the most effective of the regimens tested. This regimen of reteplase administration resulted in comparable coronary artery patency rates at 90 min to alteplase (85% vs 78%, respectively) and significantly higher patency rates at hospital discharge than alteplase (95% vs 88%, respectively). TIMI 3 flow was significantly higher in the double-bolus reteplase recipients than patients receiving alteplase at 60 min (51% vs 33%, p=0009), 90min (63% vs49%, p=0019), and at hospital discharge (88% vs 71%, p<0001). The 10MU+10MU reteplase double-bolus dosing regimen produced the highest 60 and 90 min patency rates of all the treatment regimens. Its important to emphasize that, the improved coronary artery patency with reteplase was not associated with an increased risk of bleeding or adverse clinical outcomes.

The RAPID 2 study was designed to compare coronary perfusion rates and the need for acute coronary intervention in AMI patients treated with a double bolus (10 MU+10 MU) of reteplase or 'accelerated' alteplase (15 mg bolus, 0-75mg/kg $^{-1}$ infused over 30 min, followed by 05mg/kg ^{1} infused over 60 min). The TIMI 2-3 patency and TIMI grade 3 flow rates in the reteplase group at 60 min were similar to the corresponding 90 min results in the accelerated alteplase group. In addition, significantly fewer reteplase-treated patients required additional interventions during the first 6 h post-treatment than did alteplase-treated patients (14% vs 27%, p = 0.004). Reteplase achieved significantly higher rates of early reperfusion of the infarct related coronary artery than did accelerated alteplase therapy and significantly fewer acute coronary interventions were required in patients who received reteplase therapy. Further, the relatively simple double-bolus administration of reteplase facilitated its administration compared to the relatively complex dosing infusion of alteplase.

INJECT study compared reteplase double-bolus administration with standard dose of streptokinase in 6010 patients with AMI[7]. The trial established that reteplase was as effective as streptokinase in terms of reducing mortality risk; although reteplase was associated with a positive trend toward improvement in mortality rates. Patients in the reteplase group had a significantly lower incidence of atrial fibrillation, asystole, cardiogenic shock, congestive heart failure, hypotension and all allergic reactions than patients receiving streptokinase. Complete resolution of the ECG ST-segment elevation was found in a significantly larger proportion of patients treated with reteplase than in patients treated with streptokinase. Mortality rates were 5% in the reteplase-treated group and 7% in the streptokinase-treated group.

Material and Methodology

The present study was a prospective, open-label evaluation. The objective of the study was to evaluate efficacy and safety of reteplase for patients with acute ST elevation myocardial infarction. Confirmed cases of ST elevation in myocardial infarction, reporting to corporation hospital were considered for evaluation. In all, 67 patients were selected (universal sampling). Investigations like electrocardiogram (ECG), hemogram, blood biochemistry, cardiac enzymes and echocardiography were performed as per requirement. Each patient received a total dose of 20 units of reteplase. It was given as an initial 10 units over two minutes followed by second bolus of 10 units over two minutes with the interval of 30 minutes between two boluses. Patients also received adjuvant medication (co-therapy) as part of clinical management. The efficacy and safety factors were noted in case record forms (CRFs). Patients were followed at regular intervals (30 min, 60 min, 90 min, 2 h, 6 h, 8 h, 12 h, 16 h, 24 h, subsequent follow up till discharge).

The data was entered and analyzed by SPSS software. For statistical significance, 95% confidence interval was considered.

Results

In all, 67 patients were analyzed. Successful thrombolysis was achieved in 61 patients (91.0%). Six

Table 1			
Age and sex wise distribution of patients			
Age (yrs)	Sex		Total (%)
	Male	Female	
≤ to 40	6	0	6 (9.0%)
41 to 50	25	4	29 (43.3%)
51 to 60	15	5	20 (29.9%)
> 60	9	3	12 (17.9%)
Total	55 (82.1%)	12 (17.9%)	67 (100%)

patients were referred to other hospitals for further interventions either due to continuation of chest pain (6 patients) or persistent ST segment elevation (4 patients). One (1.5%) patient died due to cardiac shock.

The age and sex wise distribution of patients is as shown in **Table 1**.

Most of patients were male (82.1%) and most (43.3%) of the patients belonged to 41 to 50 yrs age group.

Co-therapy with thrombolysistics

It was found that 66 (98.5%) patients received aspirin and clopidogrel combination as a co-therapy. Enoxaparin, nitroglycerine and anti-hypertensives were received by 92.5%, 89.5% and 83.6% patients respectively.

The time interval between chest pain and administration of thrombolytic agent is crucial for efficacy of a thrombolytic agent. **Fig. 1** represents time interval between


Fig. 1
Interval between chest pain and reteplase Administration

Table 2
Medical condition at the time of admission
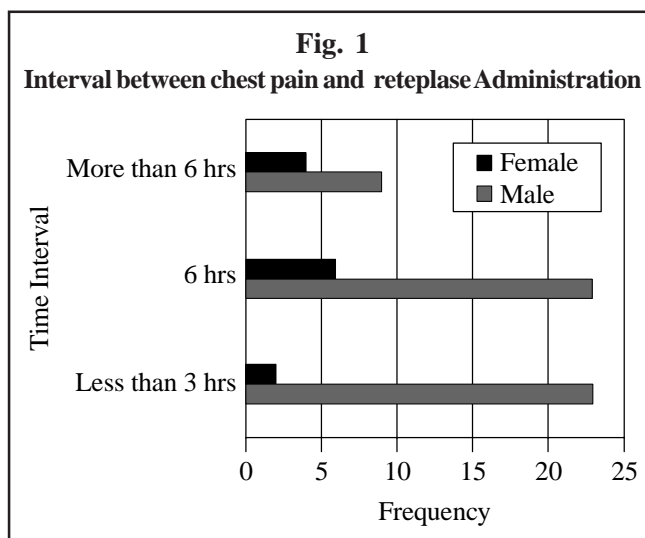
| Medical condition	Frequency
LBBB	1
HTN	7
Hyperglycemia	14

chest pain and reteplase administration. It was observed that majority (male-83.6%, female-66.6%) of patients reported to hospital in less than 6 hrs after chest pain.

Table 2 provides information about associated medical conditions at the time of presentation to hospital.

Patients were enquired and investigated for associated medical conditions which may interfere with clinical outcome. It was found that 14 patients had hyperglycemia and 7 patients had hypertension. One patient had left bundle branch block (LBBB).

Fig.2
Adverse events post reteplase administration

Table 3
Chest pain resolution
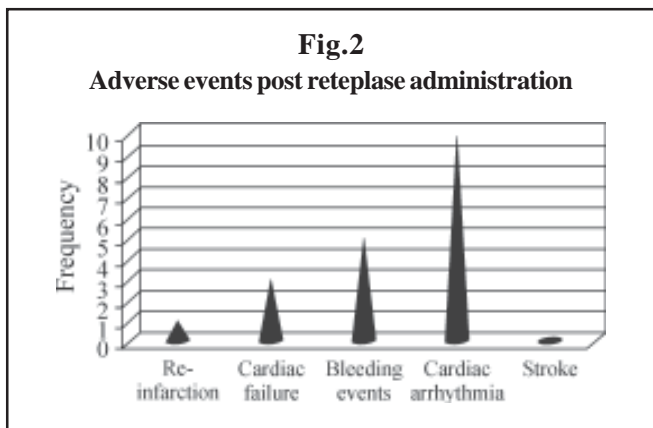
Time	Frequency	%
No resolution	6	9.0
within 1 hr	29	43.3
1 to 2 hrs	16	23.9
more than 2 hrs	16	23.9
Total	67	100.0

Fig. 3
Box whisker plot for ST segment resolution by 50% (male patients)
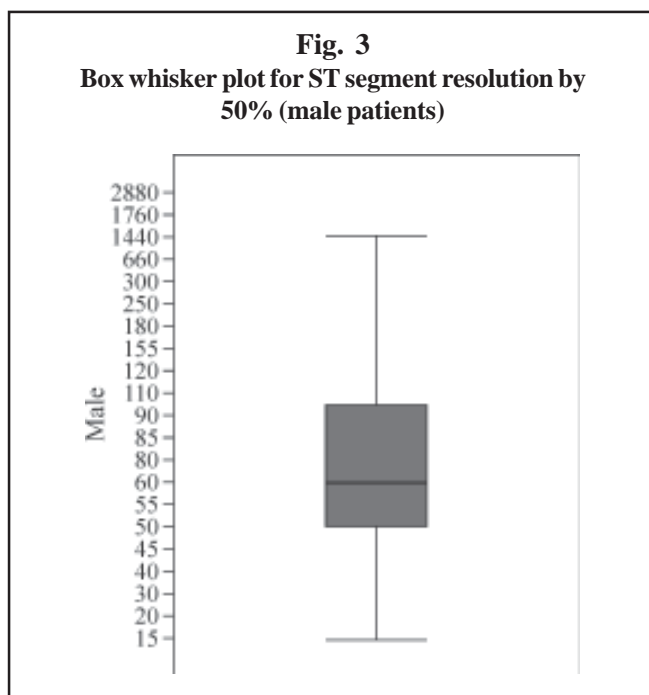
Explanation

Above Box whisker plot shows median time required for 50% ST-segment resolution in male patients. The median time was found to be approximately 60 min. The lowest time for 50% ST-segment resolution was 15 min.

The Box whisker plot shows median time required for 50% ST-segment resolution in female patients. The median time was found to be approximately 75 min. The lowest time for 50% ST-segment resolution was 15 min.

Patients were followed up for chest pain resolution. It was observed that majority (43.3%) of patients had

Table 4
ST-segment resolution (50%)

Time	Frequency	%
50% ST-segment resolution not observed	4	6.0
within 1 hr	32	47.8
1 to 2 hrs	17	25.4
more than 2 hrs	14	20.9
Total	67	100.0

Fig. 4
Box whisker plot for ST segment resolution by 50% (female patients)
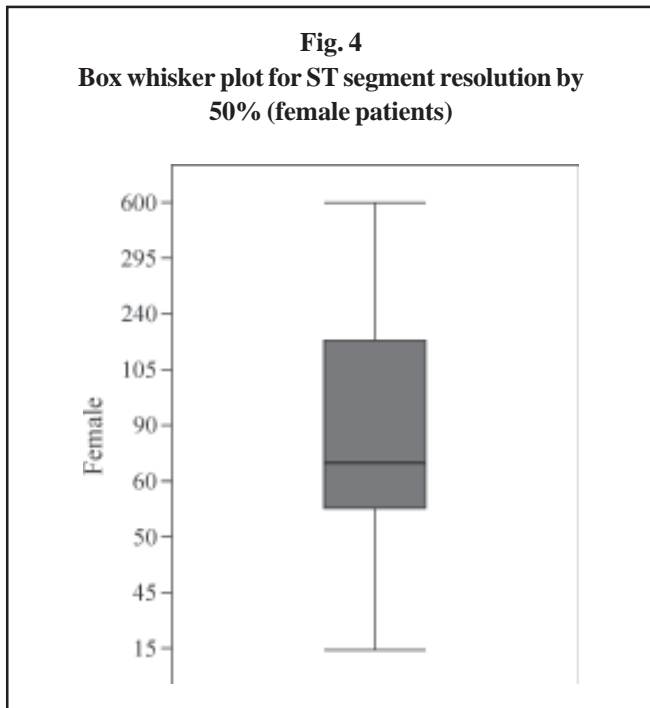
Table 5
Adverse events post reteplase administration

Adverse event	Frequency
Re-infarction	1
Cardiac failure	3
Bleeding events	5
Cardiac arrhythmia	10
Stroke	0

resolution of chest pain within 60 min. it was also found that six patients continued with chest pain, of which 2 patients had ST segment resolution, but other 4 patients continued with ST segment elevation. Patients with continued chest pain or ST segment elevation for more than 90 minutes were referred to other facility for further interventions.

It was found that 47.8% of patients had 50% ST segment resolution at the end of 60 min. Four patients had significant ST segment resolution at the end of 90 min.

Cardiac arrhythmias were observed in 10 patients. 5 patients reported with bleeding events, 4 of these events were minor (2 gastrointestinal and 2 gum bleeding), and one of these patients required platelet transfusion, who had fever 2 days prior to admission and was a suspected case of dengue fever. None of the patients had cerebral episode such as stroke.

Discussion

Patient with ST elevation myocardial infarction can be managed by percutaneous coronary intervention (PCI) or thrombolysis (fibrinolysis). The preferred reperfusion therapy in many patients with an acute ST-elevation (Q wave) myocardial infarction is primary (PCI)[8]. Thrombolytic therapy is given to eligible patients if primary PCI cannot be performed in a timely fashion. Unfortunately, thrombolytic therapy for STEMI remains underutilised. Facilitated PCI i.e. pharmacological reperfusion treatment delivered prior to planned PCI, is of crucial importance considering the time lag between chest pain and primary PCI, due to delay in transfer and limited availability of catheterization facility. Reteplase has less affinity for fibrin (more penetration of thrombus) as compared to other tissue plasminogen activators[9].

This study demonstrated that thrombolysis was successfully achieved in 61 patients (91.04%). The median time for 50% ST segment resolution in males and females was found to be approximately 60 and 75 min respectively. The overall mortality was 1.5%, which was significantly less as compared to previous global clinical trials (GUSTO-III – 7.47%, ASSET – 7.20%, INJECT – 9.02%). 32 (47.8%) patients had 50% ST segment resolution at the end of 60 minutes. Bleeding events were found in 5 (7.5%) patients, which was comparable with previous studies (GUSTO-III – 7.85%, ASSET – 11.66%, INJECT – 15.00%). One (1.5%) patient required platelet transfusion, who had fever 2 days prior to admission and was a suspected case of dengue fever. Cardiac failure was observed in 3 (4.5%) patients. Arrhythmias were reported in 10 (14.9%) patients.

Earlier studies with reteplase reported stroke events (GUSTO-III – 1.64%, ASSET – 1.10%, INJECT – 1.23%). No event of stroke was reported in present study. No other adverse events were reported.

Conclusion

Reteplase is a third generation thrombolytic agent. It is

administered as non-weight based double bolus injection. The ease of double bolus administration and non-weight based approach of thrombolysis makes it an attractive option for pre-hospital initiation of thrombolysis in patients with ST-elevation in myocardial infarction.

Present study in a primary care hospital setup confirms the efficacy and safety of reteplase. The 91.0% success rate co-relates with the efficacy of reteplase for ST-elevation in myocardial infarction. The safety parameters are comparable to that of global trials of reteplase. Reteplase administration is an effective and safe option for emergency treatment of patients with ST-elevation in myocardial infarction.

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