Efficacy and Safety of Tenecteplase (Metalyse) in Iraqi Patients with Acute ST-Elevation Myocardial Infarction

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Abstract

Background- Thombolytic therapy using tissue plasminogen activator has revolutionized the treatment of acute myocardial infarction. Tenecteplase was developed as a bioengineered variant of tissue-type plasminogen activator with specific, desirable properties. The aim of this study is to assess the efficacy and safety of tenecteplase in patients with AMI.

Methods- 50 patients with acute STEMI were enrolled in this study; those patients had presented to the hospital within 12 hours of the onset of their chest pain and fulfilled the criteria of starting thrombolytic therapy. They had been randomly selected consecutive patients from those attending the coronary care unit of Al-Yarmouk Teaching Hospital, Baghdad during the period from October 2005 to August 2006. Tenectaplase infusion over ten seconds was given according to body weight. ST-segment resolution was defined as reduction in the ST-elevation of 50% or more at 90 minutes.

Results- 40 patients (80% of the sample) were male. The range of patients' age was 28-80 years, with a mean of 54.94 ± 10.83 years and a median of 53 years old. ST- segment resolution had been observed in 27 patients (54% of the sample). The mean age of those with successful thrombolysis was 52.78 ± 10.8 years old, and 59.13 ± 10.3 years old for those who failed to respond to the thrombolytic therapy with tenecteplase. Statistical analysis revealed a highly significant effect of age on the frequency of ST-segment resolution (calculated t= 24.78, p-value <0.0001). The mean time to perfusion was 2.4 ± 2.37 hours and 4.76 ± 3.25 hours for those with successful thrombolysis and those who failed to respond, respectively. Eight out of 12 patients diagnosed with inferior STEMI had successful reperfusion. No one with double wall infarction had successful reperfusion. Two patients with diabetes (15.4%) and only 1 patient with hyperlipidemia (11.1%) had successful thrombolysis. None of those with 3 or more risk factors (7 patients) had successful reperfusion. The study showed that female patients had a higher chance of failure of thrombolysis ***(Iranian Heart Journal 2009; 10 (3):27-35).***

Key words: acute myocardial infarction ■ thrombolytic therapy ■ tenectaplase

During the last two decades, fibinolytic (thrombolytic) therapy has become the gold standard for the treatment of acute myocardial infarction.[1] In June 2000, the United States Food and Drug Administration (FDA) approved the bolus-administered agent tenecteplase, which is a recombinantly produced variant of the wild type tPA (tissue-type plasminogen activator) molecule.[2]

The modifications to wild type tPA include

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substitutions at threonine 103 (T, single-letter amino acid code), asparagine 117 (N) and at lysine 296 (K).

On the basis of the single-letter designations of these amino acid changes, this agent is also referred to as 'TNK-tPA' and this was the basis for the selection of TNKase™ as a brand name.

Tenecteplase is a genetically-engineered, multiple point mutant of tissue plasminogen activator that has a longer plasma half-life, allowing for a single bolus injection. It also has 14-times more fibrin specificity and has an 80-fold higher resistance to inhibition by plasminogen activator inhibitor than standard tissue plasminogen activator.

All currently available thrombolytic agents reduce mortality in acute ST elevation (Q-wave) MI.[3-5] There has been an overall 30 percent reduction in mortality to a value of 7-10% in major thrombolytic trials.[23] The TIMI 10A trial was a dose-ranging phase I trial in 113 patients designed to assess the pharmacokinetics, safety and efficacy of tenecteplase in humans.[6] Tenecteplase was given over 5 to 10 seconds as a single bolus of 5-50 mg; its half life was 17 minutes (compared to 3.5 minutes for alteplase).[6] TIMI 10B compared the efficacy of two doses of tenecteplase (in an attempt to determine the optimal dosing regimen) with that of alteplase in 886 patients presenting within 12 hours of symptom onset.[7] Patients were randomly assigned either 30 or 50 mg of tenecteplase over 5 to 10 seconds or 100 mg of alteplase in a front-loaded regimen over 90 minutes. The primary end point was the percentage of subjects with TIMI III flow in the culprit artery at 90 minutes after the start of treatment. Early in the trial, the 50 mg dose of tenecteplase was discontinued because of increased intracranial hemorrhage and was replaced by a 40 mg dose.[7]

ASSENT-2 trial (The Assessment of the Safety and Efficacy of a New Thrombolytic Agent Trial), directly compared tenecteplase to alteplase in 16,949 patients.[8] At 30 days there was no difference in mortality (6.2% in both groups), overall stroke rate (1.8 versus 1.7% with alteplase), or the rate of intracerebral hemorrhage (1% in both groups). However, the rate of non-cerebral bleeding complications (26.4% versus 29%) and need for transfusion (4.3% versus 5.5%) were significantly lower with tenecteplase. The improved safety profile of tenecteplase may reflect only minimal depletion of fibrinogen, and weight adjusted dosing achieved with this drug.[8] The mortality at one year remained the same with the two agents (10.2%).[9] However, the 30-day and one-year mortality among patients treated more than four hours after the onset of symptoms was lower with tenecteplase (7% vs. 9% and 12% vs. 14%).[9]

All currently available thrombolytic agents reduce mortality in acute ST elevation (Q-wave) MI. The purpose of this study was to evaluate the safety of tenecteplase in patients with AMI and its side effects by assessment of the resolution of ST- segment elevation and chest pain relief as markers for efficacy of thrombolysis.

Methods

This is a prospective study that enrolled 50 patients with acute ST-elevation myocardial infarction (STEMI) who had presented to the hospital within 12 hours from the onset of their chest pain and fulfilled the criteria of starting the thrombolytic therapy. They had been randomly selected consecutive patients from those attending the coronary care unit of Al-Yarmouk Teaching Hospital during the period from October 2005 to August 2006. All of them received thrombolysis using weight-adjusted dose of tenecteplase (Metalyse,® Boehringer Ingelheim) and subjected to full history taking and thorough physical examination. Twelve-lead ECG was taken for every patient, cardiac markers were not taken because of unavailability. ST-segment resolution had been defined as reduction in the ST-elevation of 50% or more at 90 minutes.[10,11] The data had been processed and tabulated in form of frequency

distribution tables and statistical analysis had been made using either student's t-test or chi-square test as required by the type of the data to be assessed, with selecting a p value of 0.05 as the level of significant association or effect.

Results

This study had enrolled 50 patients with acute STEMI; 40 patients (80% of the sample) were male. The range of patients' age was 28-80 years, with a mean of 54.94 ± 10.83 years old and a median of 53 years old. All of the female patients were 60 years old or older (10 patients), their age ranged between 60-76 years old (65.5 ± 6.15 years, median 64 years old). 66% of the sample (33 patients) was 60-69 years old. Fig. 1 shows age and gender distribution of the sample included in this study.

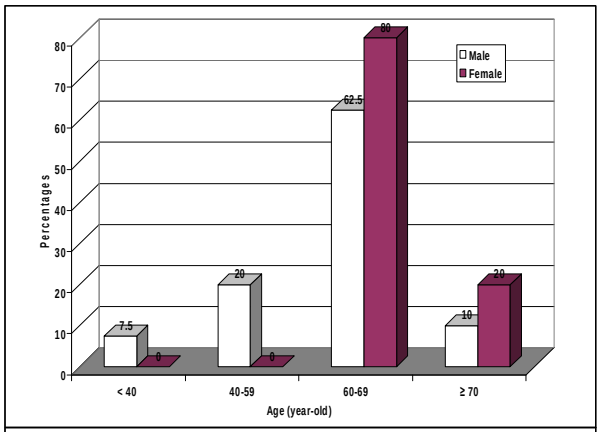

Fig. 1. Age and gender distribution of the sample.

Following thrombolysis with weight-adjusted bolus tenecteplase doses, ST segment resolution had been observed in 27 patients (54% of the sample), 24 of them were male patients (60% of male patients), while 7 out of 10 female patients (70% of females included in this study) failed to show any ST segment resolution.

Statistical analysis using Chi-square test showed a statistically significant effect of gender on the frequency of ST-segment resolution (calculated $\chi 2$ = 16.33, p value <0.0001); i.e. being female was associated with higher frequency of failure of thrombolysis.

Fig. 2 shows the frequency of ST-segment resolution according to patients' gender.

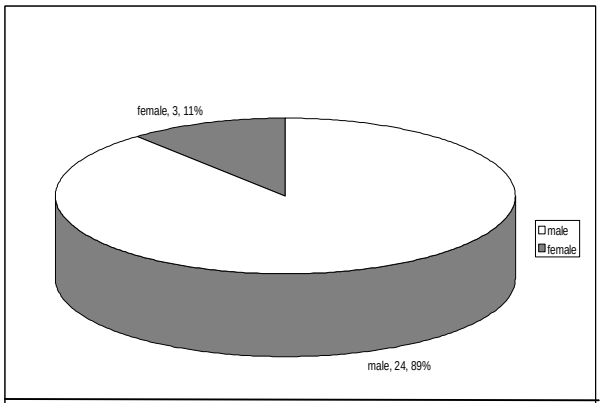

Fig. 2. Frequency of ST segment resolution according to gender.

The mean age of those with successful thrombolysis in terms of ST segment resolution was 52.78 ± 10.8 years old, and 59.13 ± 10.3 years old for those failed to respond to the thrombolytic therapy with tenecteplase. This study indicated that all of those patients younger than 40 years old showed ST-segment resolution (3 patients). On the other hand, only 1 patient out of 6 patients (16.7%) who were 70 years or older showed resolution of their ST-segment elevation with persistent ST-elevation in the remaining five patients (83.3%).

Statistical analysis revealed a highly significant effect of age on the frequency of ST-segment resolution (calculated t= 24.78, p value <0.0001).

Fig. 3 shows the patients' distribution according to their age and frequency of ST-segment resolution.

The mean time to perfusion was 2.4 ± 2.37 hours, and 4.76 ± 3.25 hours for those with successful thrombolysis and those who failed to respond, respectively.

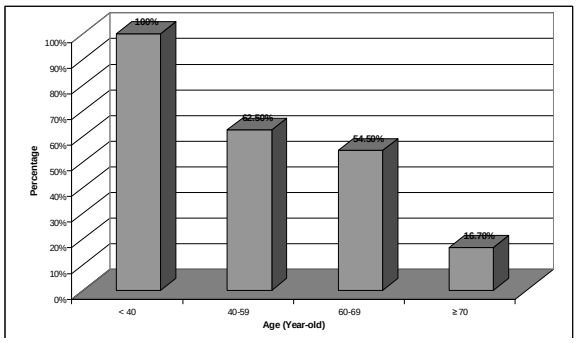

Fig. 3. Patients' distribution according to age and frequency of ST segment resolution.

22 out of 32 patients who reached the hospital within the 1st three hours of the onset of their symptoms (68.75%) had ST-segment resolution; only 1 out of 3 patients who presented within the 4th three hours (33.3%) had the same effect of thrombolysis in terms of ST-segment resolution. Statistical analysis showed that there was a significant difference in the mean of time to perfusion between those who showed or did not show successful thrombolysis (calculated t = 3.065, p value <0.005). Fig. 4 shows patients' distribution according to their time to perfusion and frequency of ST-segment resolution.

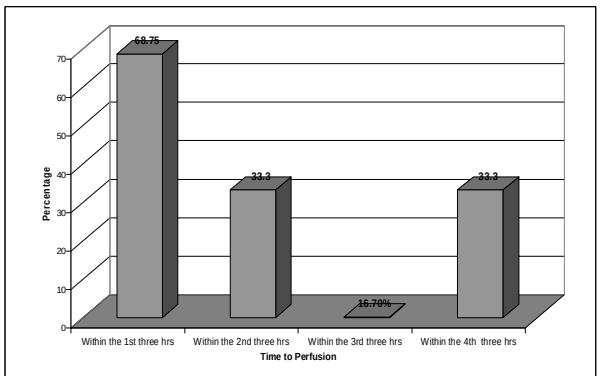

Fig. 4. Patients' distribution according to time to perfusion and frequency of ST segment resolution.

Eight out of 12 patients diagnosed to have inferior STEMI had successful reperfusion. No one with double wall infarction had successful reperfusion. Statistical analysis showed statistically significance of the type of STEMI on the frequency of ST-segment resolution (calculated X2 = 4.48, p value = 0.034). Fig. 5 show patients' distribution according to their type of MI and the frequency of ST-segment resolution.

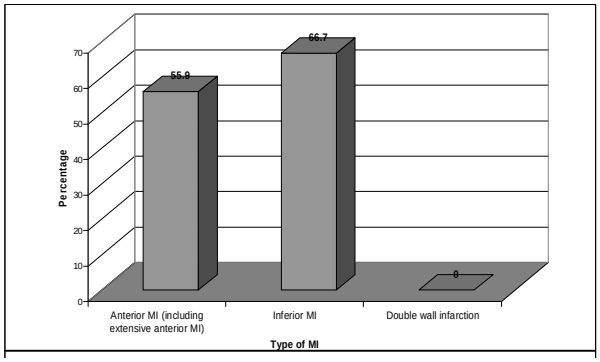

Fig. 5. Patients' distribution according to type of MI and frequency of ST segment resolution.

This study showed that 2 patients with diabetes (15.4%) and only 1 patient with hyperlipidemia (11.1%) had successful thrombolysis. Statistically significant effect of hypertension, diabetes or hyperlipidemia was seen on the frequency of ST-segment resolution. On the other hand, smoking and positive family history of ischemic heart disease had no effect on the frequency of ST-segment resolution.

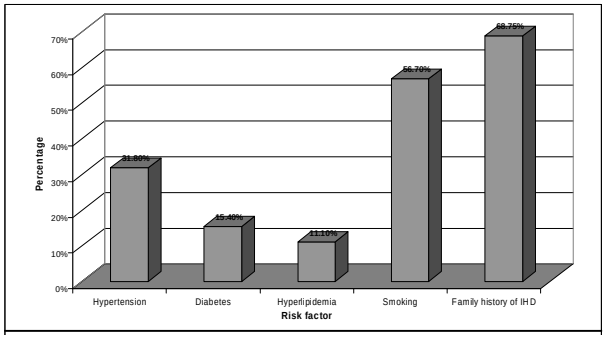

Fig. 6. Patients' distribution according to risk factors and frequency of ST segment resolution.

Fig. 6 show patients' distribution according to their risk factors and frequency of ST-segment resolution with the results of statistical analysis.

All of those with no obvious risk factor (2 patients) and none of those with 3 or more risk factors (7 patients) had successful reperfusion. Statistical analysis revealed a significant association between the number of risk factors and the frequency of ST segment resolution (calculated X2 = 8.667, p value= 0.013). Fig. 7 show patients' distribution according to the number of risk factors they had and frequency of ST segment resolution.

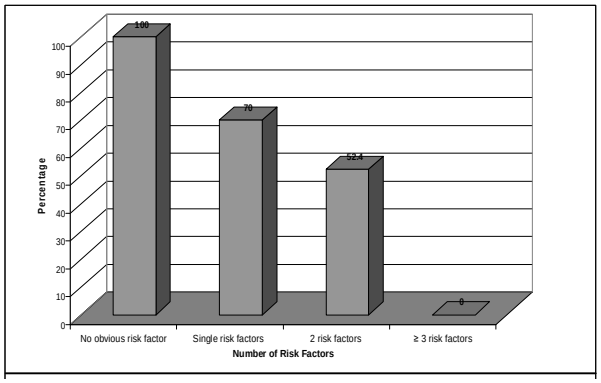

Fig. 7. Patients' distribution according to number of risk factors and ST segment resolution.

This study showed that 34 patients (68% of the sample) had no complications during their stay at hospital. Nine patients showed arrhythmias including ectopics (18%). Eight patients (16%) had mild gum bleeding, while 7 patients (14%) developed hypotension and cardiogenic shock.

Table I. Patients' distribution according to the frequency of complications observed during the study.

	No.	%
No complications	34	68
Gum bleeding	8	16
Hypotension & cardiogenic shock	7	14
Arrhythmias including ectopics	9	18

Discussion

On reviewing the results of this study, one can find that there is gradual decline in the chance of successful thrombolysis that is associated with increasing age. This is clear as all young patients showed a good response compared to failure of the ST-segment resolution within the first 90 minutes post-reperfusion that had been observed in 5 out of 6 patients whose age was 70 years or older. This inverse relationship between increasing age and reduced response to thrombolysis is statistically significant (see Table II and Fig. 3).[12] This is in agreement with other studies.[14] The aging process alone appears not to affect in any fundamental way the pathology of the culprit lesion of acute myocardial infarction, but the extent of the associated disease in the coronaries is likely to be greater and co-morbid conditions are more common.[12] Theimann et al. suggested that elderly patients, particularly those older than 70 years, may have nothing to gain from thrombolysis, indeed they may be harmed.[13] This suggestion is supported by the results of the ASSENT-II trial which showed that the 30-day mortality observed in those older than 75 years was 4-fold higher than the 30-day mortality in patients aging 75 years or younger (17.4% vs. 4.6%, respectively).[14] Furthermore, the Cooperative Cardiovascular Project had considered the age of 75 or older as an independent predictor of intracranial hemorrhage.[15] Despite these observations, the 2004 ACC/AHA guidelines concluded that age alone should not affect the decision to administer thrombolytic therapy in eligible patients without contraindications.[16]

The other interesting finding observed in this study is that the failure of achieving ST-segment resolution in 7 out of 10 female patients was statistically significant. This higher failure rate observed in female patients can be explained by the fact that all of the enrolled female patients (10 patients) were 60 years old or older and two of them were older than 70 years. This finding of higher failure

rate of thrombolysis in female patients is in agreement with the ASSENT-II trial, in which the 30-day mortality was 10% among female patients using tenecteplase compared to 5% observed among male patients.[14] In addition, the Cooperative Cardiovascular Project had considered female gender as one of the predictors for adverse outcome for thrombolytic therapy.[15]

One of the most important factors that plays a vital role in increasing the efficacy of thrombolysis is the time to perfusion. This study revealed that the best reperfusion results can be achieved if the weight-adjusted bolus dose of tenecteplase had been given within the 1st three hours (68.75% of those presented with the 1st three hours and only 33.3% of those presenting within the 4th three hours showed ST segment resolution). This difference in frequency of ST segment resolution was statistically significant (see Table III and Fig. 4).

The value of early reperfusion in patients presenting shortly after symptom onset was established by a meta-analysis of 22 thrombolytic trials including 50,246 patients.[17] The absolute benefit with thrombolytic therapy was greatest in patients treated within one hour of symptoms onset.[17] In the ASSENT-3 trial, which included 5470 patients treated with thrombolysis for acute STEMI, 25% of those treated within one hour of symptoms onset had an aborted MI, defined by no rise in serum CK levels.[18] It had been estimated that an approximate 1% reduction in mortality occurs for each hour of time saved within the 1st six hours.[19] Another important note to be mentioned here is that one study of 2948 patients found that the beneficial effect of thrombolysis on infarct size and ejection fraction was restricted to treatment given within 2 hours, while the effect on mortality can be seen when therapy is given up to 12 hours after symptoms.[20] Any longer delay results in much less myocardial salvage and functional benefit. However, unfortunately, many patients (40% in one study) present to the hospital more than 6 hours after the onset of symptoms,[21] (18% of our sample presented to the hospital more than 6 hours after symptom onset).

In regard to infarct location and its relation with the frequency of the favorable ST-segment resolution, this study showed that patients with inferior myocardial infarction showed the best response, in contrast to those with double wall infarction which showed the worst response (66.7% vs. 0% showed ST-segment resolution, respectively). In the ASSENT-II trial, anterior MI and double wall infarction was associated with a higher 30-day mortality compared to other types by nearly 2 fold (8% vs. 5%, respectively).[14] In this study all cases with inferior myocardial infarction responded to tenecteplase in terms of ST-segment resolution (8 out of 12 patients) probably because they had presented to hospital and started their reperfusion within the first three hours from the onset of their chest pain. In addition all of them had either no risk factors or just a single one.

Regarding risk factors, diabetic and hyperlipidemic patients showed very minimal response to thrombolysis (only 15.4% of diabetics, and 11.1% of hyperlipidemic patients showed ST-segment resolution), while smokers showed the best frequency of ST-segment resolution (56.7% of smokers) (see Table IV and Fig. 6).

Diabetes is a risk factor for coronary disease with diffuse involvement of the coronaries and is associated with an increased mortality in the setting of an acute STEMI. The GUSTO-1 investigators reported the results of almost 41,000 patients; 15% of them were diabetics.[22,23] Despite the similar response to thrombolysis, diabetic patients had a significantly higher mortality rate at 30 days (11.3% vs. 5.9%) and one year (14.5% vs. 8.9%) than the non-diabetics.[22,23] Similar findings were shown in the ASSENT-II trial which showed a 30-day mortality of 8.8% among diabetics using tenecteplase compared to 5.6% observed in non-diabetics[14] Although smoking promotes the development of atherosclerosis, smokers who receive a

thrombolytic agent for an acute MI have a better outcome than non-smokers.[24-29] This is comparatively similar to our study. The largest trial to evaluate the impact of smoking on outcome after thrombolysis was GUSTO-I, which showed that non-smokers had a significantly higher 30-day mortality than smokers (10.3% versus 4%).[26] This difference in outcome can be explained by the following factors:

Smokers have a better risk profile than non-smokers, particularly their tendency to be significantly younger.[30-32]

Qualitative angiographic analysis suggests that the mechanism of infarction in smokers is more often thrombosis of a less critical atherosclerotic lesion compared with non-smokers.[30] More active thrombogenic mechanisms may be operative in smokers, leading to larger thrombus component that is more susceptible to thrombolytic therapy. This may explain that the fact smokers have a higher patency rate and are more likely to have TIMI-III flow in the infarct artery after thrombolysis than non-smokers.[33]

Smokers have a variety of signs of a hypercoagulable state that may be responsive to pharmacologic intervention. These include increases in hematocrit and baseline plasma fibrinogen,[30,31] enhanced platelets thrombus formation,[34] and reduced local fibrinolytic activity,[33] the risk factors when present in the same individual patient, making those with multiple risk factors the least responsive to thrombolytic therapy.

Conflict of Interest

No conflicts of interest have been claimed by the authors.

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