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CLINICAL EVALUATION OF REPERFUSION IN ST ELEVATION MYOCARDIAL INFARCTION WITH NON- INVASIVE MARKERS FOLLOWING THROMBOLYSIS WITH STREPTOKINASE VERSUS TENECTEPLASE.

Medicine

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ABSTRACT

Background: Acute ST elevation myocardial infarction occurs due to an occluded coronary artery and can cause death of the patient. The best modality of treating an occluded coronary artery is a primary PCI. Thrombolytic therapy can however render similar results if administered within 2 hours of symptom onset. The concept of pre-hospital thrombolysis is being advocated in the face of current guidelines. Streptokinase (SK) is the most inexpensive of available thrombolytics but is fibrin non-specific, antigenic and has to be given as an infusion. Reteplase and Tenecteplase(TNK) are fibrin specific, non- antigenic and can be given as bolus doses making them good agents for prehospital thrombolysis. **Aims:** We aimed to study reperfusion after thrombolysis with streptokinase vs tenectepalse based on non-invasive criteria.**Methods:**98 patients were enrolled in this study at a tertiary care centre in a medical college in Southern India between August 2014 to August 2015. This was a non-randomised quasi-experimental study. 54 patients received streptokinase and 44 received tenecteplase in the study. **Results:** The reperfusion rate was 46.4% with streptokinase(SK) and 54.3% with Tenecteplase(TNK). Tenecteplase proved to be a better agent for patients aged more than 74 years and for patients who presented later than 2 hours. The difference between SK and TNK was not found to be significant. **Conclusion:** Tenecteplase is not superior to Streptokinase in achieving reperfusion in STEMI.

KEYWORDS

STEMI, Thrombolysis, Streptokinase, Tenecteplase, Reperfusion

INTRODUCTION

Coronary artery disease remains an important cause of mortality in our country. Acute ST elevation myocardial infarction (AMI) occurs due to occlusion of a coronary artery and can result in death of the patient. The time frame for opening an occluded coronary is as early as possible preferably in the first hour and within 120 minutes.[1] This ensures myocardial salvage and enhanced 30 day survival and survival beyond.

The two main modalities available for this purpose are thrombolytic therapy and primary PCI. There is no doubt that primary percutaneous intervention(PCI) is superior to thrombolytic therapy especially after 2 hrs of onset of AMI.[2] However thrombolytic therapy may render equivalent results if administered within first two hours.[3] Also provided that primary PCI is not readily available and requires highly specialised skill and infrastructure thrombolysis should be provided to patients if primary PCI is not available in the given time frame. The current ACC/AHA guidelines suggest thrombolysing patients with AMI if primary PCI is not available and then do PCI in these patients as soon as possible.[2] The concept of pre-hospital thrombolysis is being advocated in the face of current guidelines.

Many thrombolytic agents are available for this purpose. Streptokinase was the first agent used for this purpose and still remains easily available. It is cost effective as compared to newer agents but has issues with allergic reactions and is fibrin non-specific. The newer agents alteplase, accelerated alteplase and tenecteplase are fibrin specific and are considered relatively safer and more efficacious than streptokinase. Tenecteplase has particularly stirred interest due to its bolus administration and superiority in establishing TIMI 3 flow in infarct related artery over streptokinase however no head to head large scaled trials have been conducted between these two agents so far.[1][2][4][5]

It is important to have an open artery whatever the modality used. Coronary angiography remains the 'gold standard' for assessment of coronary patency. However, because it is associated with high cost, limited availability, and increased morbidity when performed acutely, this invasive procedure is not practical or prudent for all patients receiving thrombolytic therapy.[6]Hence there is substantial interest in noninvasive methods to identify patients in whom the coronary occlusion persists.[7] This is also important where thrombolysis may be the only modality available to treat AMI and failed thrombolysis needs to be readily identified to refer the patient promptly for rescue PCI.[8] Clinical indicators such as cessation of pain and 'reperfusion' arrhythmias have been proposed as noninvasive markers of coronary artery patency; however ,these indicators alone were found to be relatively unreliable.[9]

Other proposed criteria include ST resolution of more than 50% in the worst affected lead and peaking of cardiac enzymes within the first 12 hours after thrombolysis.[10][11][12]

In this study we aimed to study and compare streptokinase and tenecteplase as thrombolytic agents in our study using clinical, ECG and biochemical parameters of reperfusion.

MATERIALS AND METHODS:

A non-randomised quasiexperimental study was done on STEMI patients who presented to a medical college in Southern India between August 2014-August 2015 after obtaining approval from the institutional ethics committee. 98 patients were enrolled in the study who had received either streptokinase or tenecteplase in the study. The study data was analysed to address the question of whether one agent was more effective than the other in achieving reperfusion using non-invasive markers.

The aim of the study was:

1. To compare efficacy of Streptokinase and Tenecteplase in achieving reperfusion.
2. To evaluate reperfusion in ST elevation myocardial infarction following thrombolysis

Acute MI was diagnosed as per the universal definition of MI.[13]

This study included all patients diagnosed to have STEMI, thrombolysed with Streptokinase or Tenecteplase. Clinical assessment for cessation of chest pain, serial ECG's and cardiac enzymes will be done. ECG was taken at 0,2,24 and 48 hours. CPK and CKMB at 4, 12, 24 and 48hours. The following are the four criteria on which reperfusion was assessed in this study.[10][11][12][14]

1. Cessation of the chest pain
2. Regression of the ST segment by more than 50 %

3. Rapid rise and rapid fall of cardiac enzymes (CPK and CKMB)
4. Reperfusion arrhythmias

If the patient presented with(or satisfied)at least 3 of these 4 criteria, reperfusion was confirmed.

A written informed consent was taken from all subjects who were included in the study.

Inclusion criteria: All patients having STEMI, presenting with chest pain and who were not willing for a primary PCI or presented within the prescribed time frame of thrombolysis.

Exclusion criteria:
1. STEMI patients not presenting with chest pain
2. Patients having history of STEMI.
3. Patients having old myocardial infarction with aneurysm
4. Patients who had undergone coronary artery bypass surgery
5. Patients who are taken up for primary angioplasty
6. Patients with anterior wall myocardial infarction and LBBB undergoing thrombolysis.

RESULTS:

The data was analyzed using SPSS 20 software. Fishers exact test and logistic regression analysis were used to analyses the data along with percentages.

Out of the 98 patients who underwent thrombolysis, there were 79 males and 19 females.

Most patients were between the age group of 50 to 70 years (53 patients). The mean age of presentation was 58.69 years. [Table 1]

In this study out of 98 patients admitted with acute ST elevation myocardial infarction, 51(52%) had Anterior wall MI 31(31.6%) had Inferior wall MI and 16 (16.3%) with combinations.

In the present study 49(50%) patients presented within 2 hrs from which highest number of patients presented between 1-2hrs. Whereas 49 (50%) patients presented after 2hrs of onset of chest pain.

49 patients (50%) of patients had successful reperfusion with thrombolytic therapy. In this study two fibrinolytic agents were used i.e. streptokinase and tenecteplase. From the total of 98 patients 54(55.1%) received streptokinase while 44 (44.9%) were treated with tenecteplase. Out of these 25(46.3%) patients in the Streptokinase group and 24(54.5%) patients in the tenecteplase group were successfully reperfused. Hence the reperfusion rate was slightly higher in the tenecteplase group. We received an odds ratio of 1.3920 on comparison of reperfusion with tenecteplase vs streptokinase suggesting an almost 40% more favourable outcome when tenecteplase was administered as compared to streptokinase. [Table 2] however on applying the appropriate statistical tests including logistic regression this difference was not found to be significant. [Table 3]

This difference was not significant even when patients were divided as per their age and time of presentation from onset of chest pain. Patients were divided in age groups of age less than 65 years (group 1), 65-74 years (group 2) and more than 74 years (group 3) as per the GUSTO-1 trial. In patients less than 65 years 45% patients were reperfused in the streptokinase group while 55% of patients given tenecteplase were reperfused. In the age group between 65-74 years the rates of reperfusion with both streptokinase and tenecteplase were almost equal being 62.5% and 66.66% respectively. [Table 1]

It was noteworthy that in the third group that comprised of only 10 patients of more than 74 years no patient was reperfused in the streptokinase group while 33.33% patients in the tenecteplase group were reperfused. (1 out of 3 patients).

However, these results did not translate into statistical significance in either groups. But it is noteworthy that tenecteplase seems to have an edge over streptokinase in ages less than 65 years and more than 74 years more so in the latter.

The results were also studied with respect to time of onset of chest pain to thrombolysis. It was observed that in patients who presented in less than 2 hours 45.83% patients (11 out of 24) patients given tenecteplase were reperfused while 46.42% patients given streptokinase were reperfused (13 out of 28). Hence the reperfusion rates with tenecteplase were the same as streptokinase in the first two hours.

When patients presented later than 2 hours, tenecteplase reperfused 65% patients (13 out of 20), while streptokinase reperfused 50 % patients (13 out of 26). Even though this did not translate into statistical significance the difference was hard to ignore. While both agents performed equally when time of onset to presentation was less than two hours, tenecteplase did better when patients presented later than 2 hours. [Table 4]

DISCUSSION:

The management of acute MI has come a long way with the advent of primary PCI (PPCI). It is the gold standard treatment for MI provided it is available within the prescribed time frame. According to the CREATE registry PPCI is available to less than 10% of patients seeking treatment for AMI in India.[15] Hence as per ACC guidelines on STEMI management, patients with acute MI who are suitable candidates should receive fibrinolytic therapy as soon as possible ideally within first 30 minutes of medical contact.[16]

Also, where prehospital thrombolytic therapy can be administered it should be done.[3]

The first thrombolytic agent was streptokinase. However, streptokinase is fibrin non-specific, causes allergic reactions, hypotension and requires administration over 60 minutes as an infusion making it a not so suitable agent for prehospital thrombolysis.

On the other hand, the newer agents like t-PA are fibrin specific, have no issues like allergic reactions and hypotension and can be administered as bolus making them highly suitable for prehospital thrombolysis. Alteplase the first fibrin specific agent has to be given as an intravenous infusion involving a bolus followed by a two-timed infusion. Reteplase is administered as a double bolus of 10 units each over 2 minutes, half an hour apart. The dosing of reteplase does not depend on the patient's weight. Tenecteplase has to be delivered as a single bolus over 5 seconds. However, the dose needs to be calculated as per the body weight.[1][2][4][5]

In the ASSENT-3 trial subjects received 105% of the dose required and hence had more bleeding complications.[17] Also tenecteplase has higher reinfarction rates as compared to reteplase (9.3% vs 4.6%). In view of this reteplase seems to be an ideal thrombolytic agent in the current scenario.[5]

Various trials have been done to compare these newer agents with streptokinase. The GUSTO, GISSI-2 and ISIS-3 investigators compared Streptokinase and t-PA in the treatment of AMI.

The GISSI-2 trial comprised of 12,490 patients and did not show significant differences between streptokinase and t-PA in terms of combined end point of death and severe left ventricular damage (23.1% vs 22%). However higher bleeding was observed in the streptokinase group (0.5% vs 1%), almost double that of t-PA, but overall stroke rates were nearly same in both the groups.[18]

The GUSTO-1 trial compared streptokinase with accelerated alteplase. The study had four arms with 10000 patients in each arm. The study showed an absolute decrease in mortality of 1% at 30 days in favour of accelerated alteplase with heparin over streptokinase (both arms merged).[7]

GUSTO-III compared reteplase to alteplase. Reteplase was not proved to be superior to alteplase in the study.[19] It is also interesting to note that the INJECT study which was done as a comparison between reteplase and streptokinase did not show reteplase to be superior.[20]

ASSENT-2 was designed to show equivalence between tenecteplase and accelerated alteplase. There was no statistical significance with regards to mortality rate or rates of stroke however rate of major bleed was significantly less with tenecteplase (5.94% on alteplase vs 4.66% on tenecteplase.[21]

Extrapolating results from the GUSTO-I trial and ASSENT-2 trial tenecteplase can be considered superior to streptokinase.

In our study we had a 54.5% reperfusion rate with tenecteplase vs 46.3% with streptokinase. Also, patients given tenecteplase were 40% more likely to have reperfusion (OR 1.3920) proving that tenecteplase was superior to streptokinase. The reperfusion rate with tenecteplase is considered to be around 64% (TIMI 3 flow with 50 mg bolus). This was close to what we achieved in our study considering our small sample size and using non-invasive methods to re-establish reperfusion.

It is interesting to note that tenecteplase proved to be better than streptokinase in patients who were aged more than 74 years and also when patients presented two hours later from onset of chest pain. This however needs to be tested by angiographic parameters in larger multicentric studies.

However, our results were not statistically significant (p=0.310 by logistic regression analysis). It is interesting to note that even though differences have been observed between various thrombolytic agents in individual studies, a subsequent meta-analysis did not show significant differences between the various thrombolytic agents in reducing mortality.[4] A systematic review comparing older thrombolytic agents with newer ones in terms of 30 day mortality also showed no difference among them as far as 30 day mortality was concerned.[22] A similar trial conducted by Ranakishore Pelluri and colleagues reteplase to be superior to streptokinase and streptokinase superior to tenecteplase using parameters similar to ours for establishing reperfusion.[23] However that was a study of 90 patients with 30 patients assigned to each thrombolytic agent. Another study conducted in India done on 60 patients thrombolysed with streptokinase or Tenecteplase (30 in each group) which were subjected to coronary angiography after 90 minutes showed equal efficacy of both agents in achieving TIMI III flow.[24] In our study we have not studied 30 day mortality as this was not under our study design but this needs to be tested in larger controlled studies. Also, angiographic comparisons of the two groups was not carried out 90 minutes post thrombolysis due to financial and logistic constraints, which along with the small non-randomised study group were some of the limitations of our study.

In conclusion our study showed tenecteplase to be better than streptokinase in achieving reperfusion in acute MI using non-invasive parameters however a statistical significance could not be achieved. This remains an important finding in providing urgent care to patients with myocardial infarction where financial resources are restrained. The agents need to be tested in further large scale multicentric controlled studies.

Table-1 Clinical profile of patients included in the study:

SEX	
Male	79
Female	19
AGE	
< 65 years	74
65-74 years	14
>74 years	10
Type of MI	
AWMI	51
IWMI	31
Combined	16
Time of chest pain onset to presentation	
within 2 hours	49
>2 hours	49
>50% ST segment resolution	
within 90 mins.	55
more than 90 mins	43
Subsidence of chest pain	
within 90 minutes	40
>90 minutes	58
Peaking of cardiac enzymes	
4 hours	31
12 hours	38
Reperfusion arrhythmias	
present	51
absent	47
Type of thrombolytic agent used	
Streptokinase	54
Tenecteplase	44
Reperfusion status	
Reperfused	49
Non-reperfused	49

Table-2 Odds ratio of thrombolysis with Tenectepalse vs. Streptokinase

Agent used	Reperfused	Nonperfused	Total
Tenecteplase	24	20	44
Streptokinase	25	29	54
Total	49	49	98
Odds Ratio 1.390, 95% CI 0.6261-3.0946, Z stat 0.811, P-value 0.4171			

TABLE-3 Logistic regression analysis of Streptokinase(SK) vs Tenecteplase (TNK)

	B	SE	Wald	df	Significance	Exp(B)
SK/TNK	-0.4155	0.409	1.032	1	0.31	0.66
Constant	0.234	0.307	0.579	1	0.447	1.263

Table-4 Reperfusion status with tenecteplase vs. Streptokinase after 2 hours of chest pain onset

Presentation at >2hrs of chest pain	Reperfused	Non perfused	Percent Reperfused
Tenecteplase n=20	13	7	65
Streptokinase n=26	13	13	50

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