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A Randomized, Parallel Study to Compare Efficacy & Safety of Streptokinase *vs* Tenecteplase when Given in Correct Timelines in Patients of ST-Elevation Myocardial Infarction (STEMI)

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Abstract

Myocardial Infarction can be defined from a number of different perspectives related to clinical, Electrocardiographic (ECG), biochemical and pathologic characteristics. It is accepted that the term Myocardial Infarction reflects death of cardiac myocytes caused by prolonged ischaemia. The ECG may show signs of myocardial ischaemia, specifically ST and T changes, as well as signs of myocardial necrosis, specifically changes in the QRS pattern. A working definition for acute evolving Myocardial Infarction in the presence of clinically appropriate symptoms has been established as - patients with ST-segment elevation, i.e. new ST-segment elevation at the J point with the cut-off points >0.2 mV in V1 through V3 and >0.1 mV in other leads. ST-elevation appears in ECG due to full thickness damage of cardiac muscle. Thus, STEMI is more severe type of myocardial infarction compared to NSTEMI (Non-ST elevation myocardial infarction) in which partial thickness damage of heart muscle develops. The most common symptom of MI is chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw. Often it is in the center or left side of the chest and lasts for more than a few minutes. Other symptoms may include shortness of breath, nausea, feeling faint, a cold sweat, or feeling tired. Patients of STEMI should be considered for primary PCI (Per-Cutaneous Coronary Intervention) immediately. It is the main treatment of choice for ST-segment elevation myocardial infarction. It reduces mortality rate, infarct size and further re-infarction. But if PCI is not available of primary PCI cannot be performed within 120 minutes of diagnosis then fibrinolytic therapy is the best option. PCI is superior to fibrinolytic therapy in circumstances where there is an immediate access to skilled facility and physician/health care teams. If this is not available, then fibrinolytic therapy is an effective alternative. The benefits of thrombolytic therapy in patients with acute myocardial infarction are well established. The benefit of thrombolytic therapy is very time dependent. Major benefit is seen in those patients who present within 3 hr of the onset of symptoms. Thrombolytic therapy can also be administered to the patients presenting within 12 hr of symptoms. Thrombolytics recanalize thrombotic occlusion associated with ST-segment Elevation Myocardial Infarction (STEMI) and restoration of coronary flow reduces infarct size and improves myocardial function and survival over the short term and long-term. Complete restoration of coronary flow is the principal mechanism by which reperfusion therapy improves survival and other clinical outcomes in subjects with acute myocardial infarction in whom there is electrocardiograph evidence of ST-segment elevation. Intravenous thrombolytic therapy is, however, the standard of care for subjects with acute myocardial infarction, because of its widespread availability, its ability to reduce mortality, and its use in more than a million subjects over the past decade.

Keywords: Streptokinase; Tenecteplase; STEMI; TIMI Flow

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Introduction

Acute Coronary Syndrome is a syndrome due to decreased flow in the coronary arteries so that the part of heart muscle (myocardium) is unable to function properly and thus it dies. Most common symptom is chest pain, often radiating to the shoulder or angle of the jaw, associated with nausea and sweating. Acute Coronary Syndrome is caused by one of the three problems: ST-elevation Myocardial Infarction (STEMI, 30%), non ST-elevation Myocardial Infarction (non-

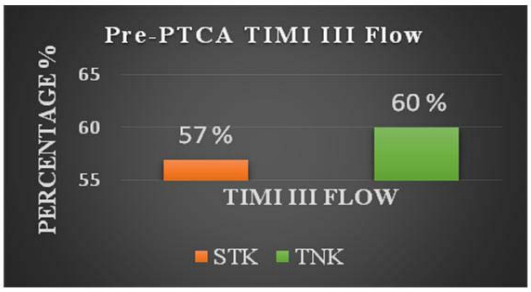

Figure 1: TIMI III Flow prior to PTCA.
Interpretation: As per above graph, in STK group 57% population was having TIMI III flow after 90 min CAG (Prior to PTCA) and in TNK group 60% population was having TIMI III flow after 90 min CAG (Prior to PTCA).

Figure 2: TIMI III Flow after PTCA.
Interpretation: As per above graph, in STK group 100% population was having TIMI III after PTCA and in TNK group 100% population was having TIMI III flow after PTCA.

STEMI, 25%) or Unstable Angina (38%) [1].

Myocardial Infarction can be defined from a number of different perspectives related to clinical, Electrocardiographic (ECG), biochemical and pathologic characteristics. It is accepted that the term Myocardial Infarction reflects death of cardiac myocytes caused by prolonged ischaemia [2].

The ECG may show signs of myocardial ischaemia, specifically ST and T changes, as well as signs of myocardial necrosis, specifically changes in the QRS pattern [2]. A working definition for acute evolving Myocardial Infarction in the presence of clinically appropriate symptoms has been established as - patients with ST-segment elevation, i.e. new ST-segment elevation at the J point with the cut-off points >0.2 mV in V1 through V3 and >0.1 mV in other leads. ST-elevation appears in ECG due to full thickness damage of cardiac muscle. Thus, STEMI is more severe type of myocardial infarction compared to NSTEMI (Non-ST Elevation Myocardial Infarction) in which partial thickness damage of heart muscle develops [3].

The most common symptom of MI is chest pain or discomfort which may travel into the shoulder, arm, back, neck, or jaw. Often it is in the center or left side of the chest and lasts for more than a few minutes. Other symptoms may include shortness of breath, nausea, feeling faint, a cold sweat, or feeling tired.

The benefits of thrombolytic therapy in patients with acute myocardial infarction are well established. The benefit of thrombolytic therapy is very time dependent. Major benefit is seen in those patients who present within 3 hr of the onset of symptoms. Thrombolytic therapy can also be administered to the patients presenting within 12 hr of symptoms. Thrombolytics recanalize thrombotic occlusion associated with ST-segment Elevation Myocardial Infarction (STEMI) and restoration of coronary flow reduces infarct size and improves myocardial function and survival over the short term and long-term. Complete restoration of coronary flow is the principal mechanism by which reperfusion therapy improves survival and other clinical outcomes in subjects with acute myocardial infarction in whom there is electrocardiograph evidence of ST-segment elevation. Intravenous thrombolytic therapy is, however, the standard of care for subjects with acute myocardial infarction, because of its widespread availability, its ability to reduce mortality, and its use in more than a million subjects over the past decade [4].

Thrombolytic therapy is easily and quickly administered and is readily available; it requires little skill or equipment, and yields greater benefit the sooner it is given after the onset of symptoms.

Streptokinase (STK) is a thrombolytic medication and enzyme. As a medication it is used to break down clots in some cases of myocardial infarction (heart attack), pulmonary embolism, and arterial thromboembolism. The type of heart attack it is used in is an ST Elevation Myocardial Infarction (STEMI). It is used intravenously. Side effects include nausea, bleeding, low blood pressure, and allergic reactions [5].

Tenecteplase is a variant of the native tissue-type Plasminogen Activator (tPA) molecule that has 14-fold greater fibrin specificity than alteplase, a longer half-life, slower plasma clearance, and 80-fold greater resistance to inhibition by plasminogen activator inhibitor type 1. Its half-life of approximately 18 min allows single-bolus administration. In comparative clinical trials, tenecteplase was found to have equivalent efficacy to recombinant tPA (alteplase). The rate of intracranial hemorrhage with tenecteplase was similar to that with alteplase, and tenecteplase was associated with fewer noncerebral complications and less need for blood transfusions [6,7].

Methods

Study population and methodology

This study was a single-center, randomized and parallel study consisted of male and female subjects aged 18-65 years with ST Elevation Myocardial Infarction (STEMI) of less than 6 hours duration admitted to ICCU. We screened and enrolled 60 subjects in the study (30 in Streptokinase group and 30 in Tenecteplase group). The information regarding clinical trials in general and then information's in detail about the study given to patients and their relatives.

The Informed Consent Form was prepared in Marathi, Hindi and English languages for better understanding of the patient and the relatives. ICF were designed in English language and then translated from English to Marathi for understanding purpose of the patients. Questionnaire was drafted according to understanding of the people in the area of Nashik. The information gathered from patient's in-patient course included: Age, Sex, Height, Weight, BMI, Past history, Personal History, Date of Admission, Time of onset of Symptoms, Time of Admission, Symptoms to door time, Thrombolytic agent, Thrombolysing time, Door to thrombolysing time, Thrombolisation to needle time (CAG Time), CAG result, Flow Achieved, PTCA date, Flow achieved after PTCA, LVEF assessed by ECHO. Further data collected was interpreted and analyzed using various statistical methods and obtained the final results or endpoints of the study. The data collection process was done in the in-patient course of the patient. Source used for that was IPD papers, lab reports, CAG report,

Figure 3: Mortality Rate at day 30.
Interpretation: As per above graph, in STK group 0% population was having Mortality Rate at day 30 and in TNK group 0% population was having Mortality Rate at day 30.

Figure 4: ST-resolution Pre-PCI (at 90 min)
Interpretation: As per above graph, in STK group 73.3% population was having ST-resolution Pre-PCI and in TNK group 76.6% population was having ST-resolution Pre-PCI.

PTCA report, ECHO report, ECGs.

After Signing of ICF, medical history of subjects was taken. Subjects having history of Stroke, LBBB, tumor, hypertension, contraindication to thrombolytics, women of childbearing capacity or lactating women were excluded from study. Clinical examination, Lab investigations, ECG and ECHO of subjects were done. Drug administration was done to subjects according to the body weight by IV route. Door-to-needle time (Thrombolisation Time) was documented. After 90 min of drug administration, coronary angiography of subjects was performed. Perfusion grades (TIMI flow) and procedural details were noted. Subjects' clinical status was noted till the time of discharge. Follow-up of subjects were done on day 7, day 30 and day 60.

Data collection and statistical analysis

It was an observational and data collection study where the data was entered into excel spread sheet where the data was analyzed and shown in charts, tables and pie charts as applicable.

The results were obtained from total number of respondents i.e. n=60, the data was entered in excel spreadsheet and analyzed using tables, diagrams, pie charts and suitable statistical tests as applicable. Total numbers of participants were 60; the data analyzed for the following parameters: Date of Admission, Time of onset of Symptoms, Time of Admission, Symptoms to door time, Age, Sex, Height, Weight, BMI, Past history, Personal History, Thrombolytic agent, Thrombolysing time, Door to thrombolysing time, Thrombolisation to needle time (CAG Time), CAG result, TIMI Flow Achieved, PTCA date, Flow achieved after PTCA, LVEF assessed by ECHO.

Results

In STK group 57% population (in 17 subjects) was having TIMI III flow after 90 min CAG (Prior to PTCA) and in TNK group 60% population (in 18 subjects) was having TIMI III flow after 90 min CAG (Prior to PTCA). In both STK and TNK group in 100% population (in 30 Subjects) TIMI III Flow was obtained after PTCA. However, In STK group 43% population (in 13 subjects) was having TIMI II flow after 90 min CAG (Prior to PTCA) and in TNK group 40% population (in 12 subjects) was having TIMI II flow after 90 min CAG (Prior to PTCA). Mortality rate was nil for both the groups on day 30 and day 60. In STK group, 73.3% population was having ST-resolution at 90 min before PTCA and in TNK group 76.6% population was having ST-resolution at 90 min before PCI. No major bleeding events were observed in both the groups. However, minor bleeding events were observed in population of both STK and TNK group. Ejection Fraction assessed by Echocardiography was significantly improved in both the groups after PTCA.

Discussion

In present study, population included was the patients admitted to hospital within 6 hr of symptoms of STEMI in the period of Aug 2016 to Mar 2017 (8 months). The data was collected in the month of January, February and March 2017.

The study population was consisted of male or female subjects aged 18-65 years with ST Elevation Myocardial Infarction (STEMI) of less than 6 hours duration admitted to ICCU. Total 60 subjects were enrolled in the study, 30 subjects in Streptokinase group and 30 in Tenecteplase group.

As per collection of the data in the study, primary endpoint was

Figure 5: ST-resolution Post-PCI.
Interpretation: As per above graph, in STK group 96.6% population was having ST-resolution Post-PCI and in TNK group 96.6% population was having ST-resolution Post-PCI.

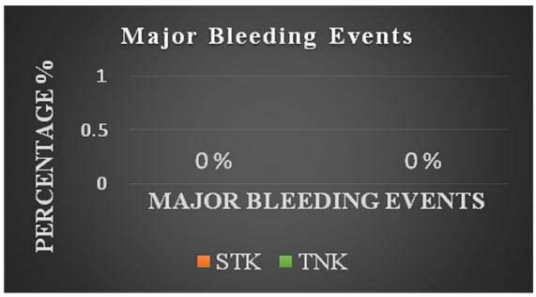

Figure 6: Major Bleeding events.
Interpretation: As per above graph, in STK group 0% population was having Major Bleeding events and in TNK group 0% population was having Major Bleeding events.

to achieve TIMI III flow in Coronary Angiography done after 90 mins of STK or TNK administration. The results of Coronary Angiography were observed and results showed that TIMI III flow was obtained in 57% population in group of subjects administered with STK and in 60% population TIMI III flow was observed in subjects administered with TNK. As TIMI III flow was primary endpoint of the study, it shows that in both groups similar efficacy is obtained. Thus, STK is as effective as TNK in patients of STEMI when given in correct timelines [8].

Another primary endpoint of the proposed study was mortality rate on day 30. As per results, no mortality was seen in both groups on day 30. Thus, mortality rate was nil for both STK and TNK groups. Therefore, this shows that STK is as safe as TNK when given in correct timelines in patients of STEMI [9].

Secondary endpoints of the study were ST-resolution before PCI (at 90 minutes) identified on ECG of subjects. However, in STK group, ST-resolution obtained in 73.3% population before PCI and in TNK group 76.6% population was having ST-resolution before PCI. This also proves that STK is as effective as TNK to resolve ST elevations caused as a result of STEMI [10].

In both STK and TNK groups, no major bleeding was observed during the in-patient course of subjects in the study. Thus, bleeding rate was nil for both the groups [11]. Minor bleeding was observed in STK group in 6.6% population and in TNK group in 3.3% population. Bleeding is the common side effect of the thrombolytics. In both the groups, bleeding observed was minor and subjects' general condition was stable at the time of discharge.

Left Ventricular Ejection Fraction (LVEF) was one of the secondary endpoint of the study. LVEF was assessed in subjects of both groups before PCI and after PCI. LVEF was separately assessed in subjects having AWMI or IWMI.

LVEF was significantly improved in both STK and TNK groups after PCI in both AWMI and IWMI subjects.

The cost is one another important issue here. As streptokinase is much cheaper than the tenecteplase, it helps to treat the patients of Acute Myocardial Infarction with the similar way as that of tenecteplase when given in correct timelines [12-15].

Conclusion

Efficacy & Safety of Streptokinase *vs*. Tenecteplase when given in correct timelines in patients of ST-Elevation Myocardial Infarction (STEMI) was much similar. When STK is given within correct timelines in patients of STEMI, then STK is similar in efficacy and safety as that of TNK.

TIMI III flow obtained in the group of patients' thrombolysed with STK is similar to group of patients' thrombolysed with TNK. In STK group 57% population got TIMI III flow prior to PCI whereas 60% population got TIMI III flow prior to PCI in TNK group. However, post-PCI TIMI III flow was equal in both groups (In patients' thrombolysed with STK as well as in patients' thrombolysed with TNK). The primary objective of the study was all-cause mortality rate on day 30 which was nil in both patients' thrombolysed with STK as well as in patients' thrombolysed with TNK group.

Evaluation of safety was done based on adverse events, physical exams, vital signs, ECGs, ECHO and safety laboratory tests at study visit (Day 30). No any major adverse events or bleeding events were observed during the hospitalization of patients in both groups. Also, according to the assessment done on day 30, no major adverse events were noted in patients of both the groups.

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