Thrombolytic Effect of Streptokinase Infusion Assessed by ST Segment Resolution between Diabetic and Non Diabetic Myocardial Infarction Patients

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Recently, it has been hypothesized that type 2 diabetes might interfere with acute intravenous thrombolytic effectiveness as estimated by angiographic or electro cardiographic criteria. This prospective study was carried out to compare the thrombolytic effect of streptokinase between diabetic and non diabetic myocardial infarction patients. Out of 200 study subjects with acute ST segment myocardial infarction (STEMI), admitted at coronary care unit, Diabetic Association Medical College Hospital and classified into diabetics (N = 79) and non diabetics (N=121). Streptokinase was given to each patient at a dose of 1.5 million units in 1 hour. Twelve lead E.C.G was recorded immediately before the start of thrombolytic therapy and at 90 min afterwards for the patients with STEMI. The ST segment elevation resolution was calculated and stratified as complete resolution (>70% ST resolution), partial resolution (30% – 70% ST resolution), or failed resolution (<30% ST resolution). Complete ST resolution occurred in 19.0% of diabetic and 50.4% of non diabetic patient, respectively ($p<0.001$). The incidence of parital ST resolution in diabetic and non diabetic patients was 12.7% and 31.4%, where as 68.4% of patients in the diabetic group and 18.2% of patients in the non diabetic group showed failed ST resolution. ST resolution was independent of the location of MI. Failure of ST segment resolution 90min after streptokinase infusion is notably higher in diabetic vs non diabetic patients. It may be concluded that diabetes mellitus might affect the thrombolytic outcome of acute myocardial infarction patients with diabetes mellitus.

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Key words: Streptokinase, diabetes, acute myocardial infarction, thrombolysis.

Introduction

The main purpose of thrombolysis in acute myocardial infarction (MI) is early and complete reperfusion. Therefore, incomplete or delayed reperfusion is associated with an increased risk of death and left ventricular (LV) dysfunction. The time to reperfusion and complete reperfusion remain the key determinants for appropriate outcome of cardiovascular events. Acute myocardial infarction may be considered as a

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potential epidemic for mankind.[1] Incidence of coronary disease is increasing in Bangladesh.[2] Death rates from coronary heart disease in UK are among the highest in the world but are falling now[3]. However, South Asians living in the UK and Canada do not display high rates of smoking, hypertension, or elevated cholesterol but still have higher rates of coronary artery disease compared with Europeans.[4]

The acute coronary syndromes include ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina. Diabetes mellitus is one of the six primary risk factors identified for myocardial infarction, others are dyslipidemia, hypertension, smoking, male gender, and family history of atherosclerotic arterial disease. Diabetes is a dyslipidemic disease and increases the rate of atherosclerotic progression of vascular occlusions.[5]

Among patients with an acute myocardial infarction, 10-25% has diabetes.[6] Even when promptly receiving thrombolytics the outcome in diabetic subjects is still worse than non-diabetics manifesting impaired post-thrombolysis left ventricular function and prognosis.[7]

Currently available fibrinolytic agents that dissolve vascular thrombi are: a) nonselective fibrinolytic agent (streptokinase, anistreplase, urokinase) and b) recombinant tissue-type plasminogen activator (alteplase, duteplase, reteplase).

Streptokinase was the first thrombolytic drug to be described and introduced in the treatment of myocardial infarction since 1958.[8] However, newer fibrinolytic agents are equivalent but not superior to older non-selective agents.[9]

Use of streptokinase in patients with acute myocardial infarction is considered up to 12 hours after the onset of chest pain.[10] But it is the 1st hour considered golden hour for thrombolytic therapy. The outcome of acute myocardial infarction treated with fibrinolytic therapy can be evaluated either by coronary angiographic measurement of TIMI (Thrombolysis In Myocardial Infarction) blood flow or by the measurement of ST segment resolution at 90 min after streptokinase infusion, in 12 lead electrocardiogram[7]. Although successful recanalization of the epicardial vessel is a necessary condition, it is the micro-vascular flow that most strongly correlates with outcome. ST segment changes reflect myocardial rather than epicardial flow and hence yield prognostic information beyond that provided by coronary angiogram alone.[11,12] ST segment resolution within 90 min is a simple measure of assessing reperfusion in patients receiving fibrinolytics.[13]

Mortality after acute myocardial infarction in patients with diabetes is about twice that of nondiabetic patients[14]. It is uncertain whether this difference in mortality is due to a lower rate of successful thrombolysis, increased re-occlusion after successful thrombolysis, greater ventricular injury or more adverse clinical profile in diabetic patients.

In Bangladesh, 90-95% of all diabetes patients belong to type 2 diabetes.[15] Current thrombolytic treatment of acute myocardial infarction, derived from large clinical trials has dramatically improved survival in both non-diabetic and diabetic patients. However despite these improvements, diabetes still doubles the fatality rate. As because diabetes profoundly affects cardiovascular disease, one could argue that clinical trial with potential implications for the care of patients with ischemic heart disease, should be specifically

designed to evaluate the effect of thrombolytic therapy in diabetic patients.

Thus it is hypothesized that type 2 diabetes might. Interfere with the effectiveness of acute intravenous thrombolysis, as estimated by angiographic or electrocardiographic criteria.[16] In the current study, we compared the thrombolytic effect of streptokinase between diabetic and non diabetic MI patients.

Methods

In a prospective study, 200 consecutive patients who were admitted in coronary care unit at Diabetic Association Medical College Hospital, Faridpur between April 2012 and April 2014 with typical chest pain or other clinical manifestations of MI within 6hrs of onset of chest pain were included into the study. The final diagnosis of STEMI was confirmed using electrocardiogram (E.C.G) special changes and elevated cardiac enzymes that were checked at the admission time. Included patients had the following criteria:-

i) Typical chest pain lasting ≥ 30 min.

ii) ST segment elevation ≥ 0.2 mv in two or more contiguous precordial leads (for the diagnosis of anterior wall MI) or in leads V1-V3 (for the diagnosis of anteroseptal wall MI) as well as ≥ 0.1 MV in II, III and aVF leads (for the diagnosis of inferior wall MI) on the admission E.C.G

iii) Increase in serum creatinine kinase (CK) level more than twice the normal value.

Inclusion criteria - patients with STEMI came within 6 hrs of chest pain, known diabetic or established during hospital stay by repeated blood glucose estimation.

Exclusion criteria - were late presentation, more than 6 hrs since the onset of chest pain, history of previous MI, not treated with streptokinase, or left bundle branch block (LBBB) pattern in E.C.G.

Streptokinase was given to each patient at a dose of 1.5 million units, diluted in 100 ml of normal saline in 1 hour. Informed written consent of the patient/attendant was taken. Twelve lead E.C.G was recorded immediately before the start of thrombolytic therapy and 90 min afterwards for the patients with STEMI. Fasting plasma glucose was recorded from all patients on the morning of the day following hospital admission. For differentiating new case of diabetes, stress hyperglycemia and non diabetic, fasting plasma glucose measurements were repeated in stable condition prior to discharge from hospital. Complications like hypotension, shock, hemorrhagic manifestation following streptokinase were noted.

In normal 12-lead ECG, ST segment lies between QRS complex and the T wave. The normal ST segment begins at the J point, the first point of inflexion on the upstroke of the S wave and is situated on the iso-electric line-that is at the same level to the part between T wave and next P wave.[17]

Elevation of ST segment occurs during acute myocardial infarction, which returns to the isoelectric line within 48 to 72 hours if not treated with thrombolytics. Reduction of height of ST segment elevation (ST resolutions) towards baseline within 90 minute after streptokinase infusion has been shown to be a useful predictor of successful reperfusion[18]. The ST-segment elevation resolution stratified by,[19] into 3 categories: a) complete ST resolution (≥70% reduction of ST elevation), b) partial ST resolution (<70% to 30% reduction of ST elevation), and c) failed ST resolution (<30% reduction of ST elevation).

The ST-segment elevation resolution was calculated as the initial sum of ST-segment elevation (on pre-treatment ECG) minus the sum of ST-segment elevation on the second

ECG (90 min after streptokinase infusion) divided by the initial sum of ST-segment elevation and expressed as percentages.[19] Complete ST resolution (≥70% ST-resolution) in patients with acute myocardial infarction, most likely identifies patients with successful reperfusion following streptokinase therapy and these patients proved to be a very low-risk group with good prognosis whereas failed or no ST-resolution (<30% ST resolution) identifies patients with failed myocardial reperfusion, which means that these patients have a higher risk for an adverse outcome. However, parital ST resolution (<70% to 30%) is related to impairment of reperfusion at the myocardial level reflecting the unpredictable effect of streptokinase.[20-21]

Twelve-lead ECG was recorded immediately with preformed data collection sheet- 1) by observation, 2) by clinical examination, 3) ECG and 4) biochemical examination (fasting blood glucose). All statistical analyses were done by SPSS version.[12] The $p<0.05$ was taken as level of significance. Unpaired t- test, Z proportion test and chi-square test (×2) were done where applicable.

Results

Grouping of study subjects, sex distribution, socio-economic and risk factors characteristics were presented in table 1. Diabetics were older than the non diabetic participants and the history of hypertension was more prevalent in the former group. The overall prevalence of current smoking was higher in the non diabetics. The two study groups were matched with respect to age, sex, socio-economic status, family history of coronary artery disease and associated other risk factors.

Table I: Baseline characteristics of diabetic and non diabetic myocardial infarction patients

Characteristics	Diabetic (n=79)	Non diabetic (n=121)
Age (mean ± SD)	52.2 ± 9.5	47.5 ± 9.2
Number of male	60 (75.9%)	89 (73.6%)
Number of female	19 (24%)	32 (26.4%)
Current smoking (positive smoking history)	41 (51.9%)	87 (71.9%)
F/O of CAD	20 (25.3%)	46 (38.0%)
Dislipidaemia	34 (43.0%)	31 (25.6)
History of HTN	50 (63.3%)	58 (47.9%)
CKD	8 (10.1%)	5 (4.1%)
Time of thrombosis after admission (mean ± SD) hr	4.85 ± 2.5	5.65 ± 1.5

CAD= Coronary artery disease
CKD= Chronic kidney disease

Anterior MI appeared in 31.7% of the diabetic and 28.9% of the non diabetic patients. Inferior MI was similarly observed in diabetic and non-diabetic groups (Diabetics 50.6% vs non diabetics 52.1%,). Anteroseptal MI appeared in 17.7% of the diabetic and 19.0% of the non diabetic patients (fig 1).

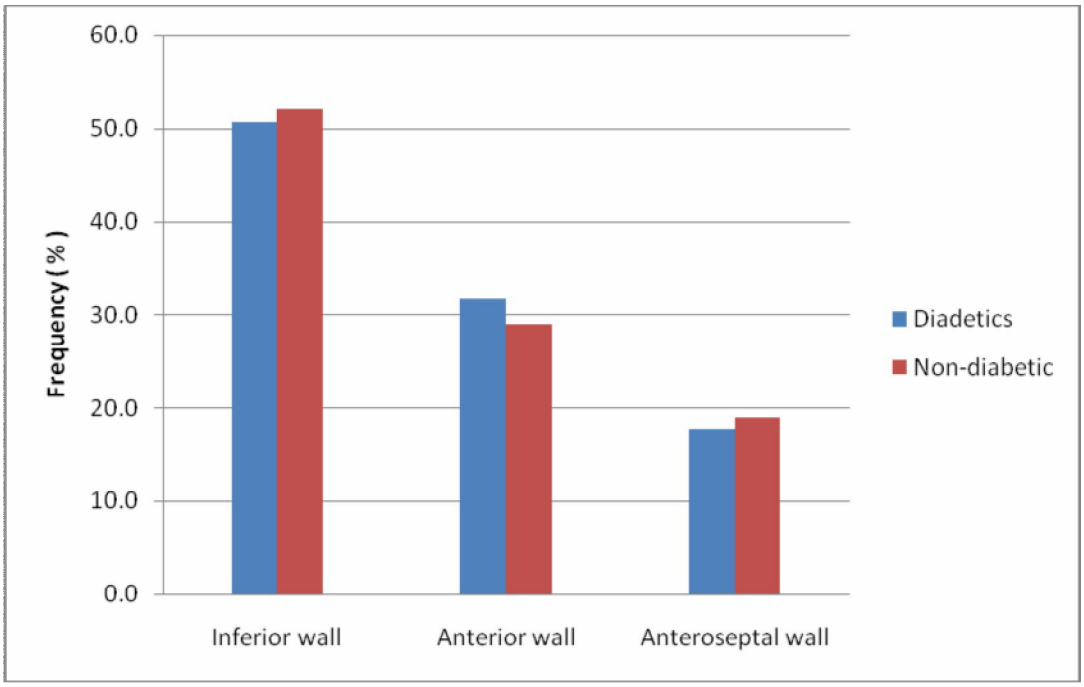

Figure 1. Location of the myocardial infarction (MI) in diabetes and non-diabetes.

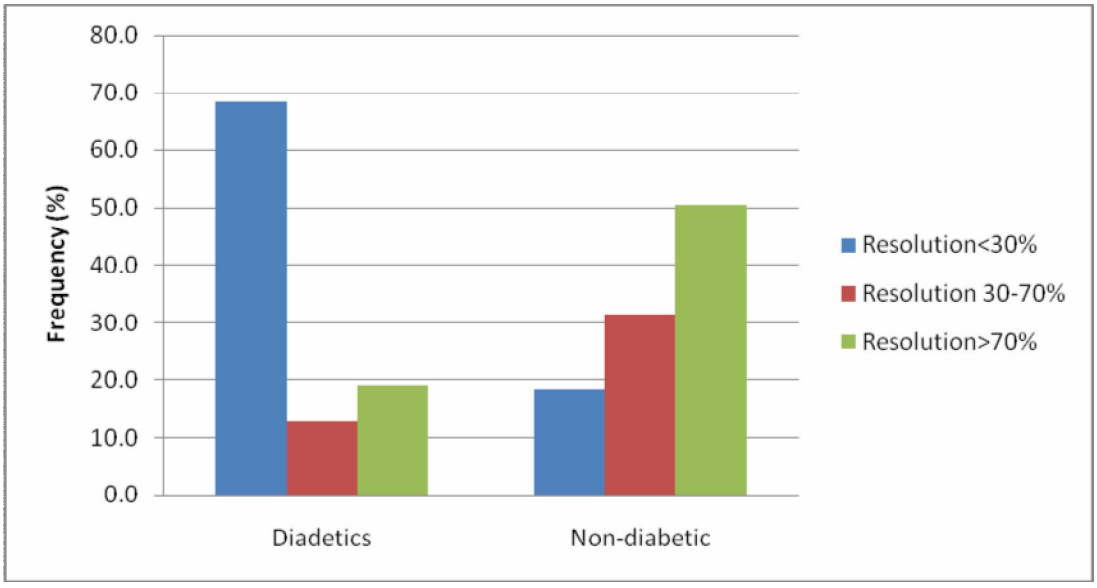

Figure 2. ST-segment resolution in diabetes and non-diabetes

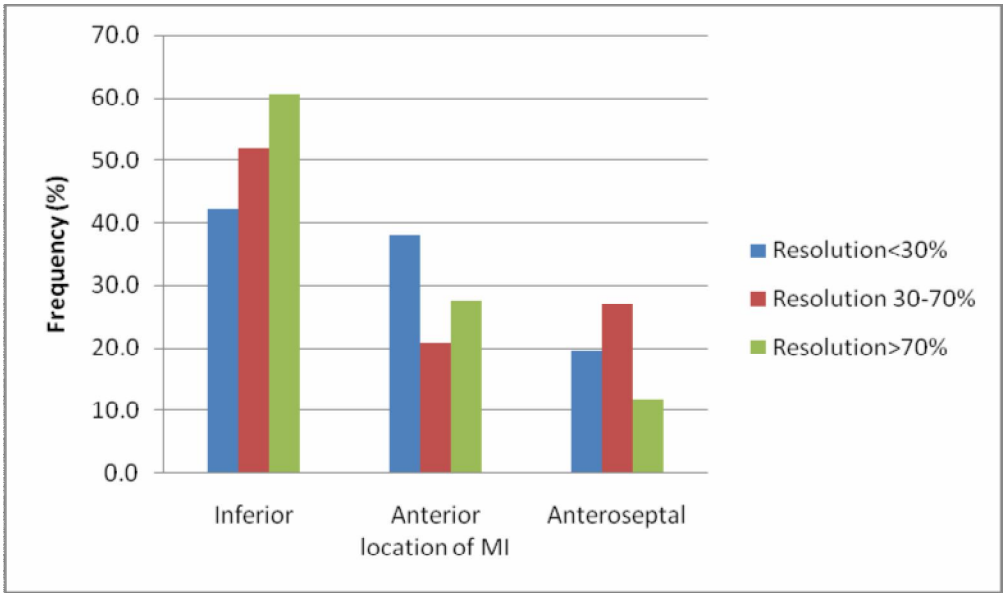

Figure 3. ST-segment resolution in different locations of myocardial infarction (MI).

Table II: Streptokinase infusion related complications in DM and non DM MI patients

Complications	Diabetic patients (n=79)	Non-diabetic patients (n=121)	Percentage (%)
Hypotension	22	32	DM-(27.8%) Non DM-(26.4%)
Shock	6	8	DM-(7.6%) Non DM-(6.6%)
Hemorrhagic manifestation	4	6	DM-(501%) Non DM-(4.9%)

A comparison of ST resolution at 90 min after streptokinase between DM and non- DM myocardial infarction patients where complete ST resolution occurred in 15 (19.0%) of diabetic and 61 (50.4) of non diabetic patients respectively ($p < 0.001$) (fig 2). The incidence of partial ST resolution in diabetic and non diabetic patients was 10 (12.7%) and 38 (31.4%) where 54 (68.4%) patients in diabetic and 22 (18.2%) Patients in non diabetic showed failed ST resolution. ST resolution was independent of the location of MI, chi-square (×2) test was done to assess the influence of diabetes on the efficacy of streptokinase, by evaluating differences of ST resolution between diabetic and non diabetic subjects. There was significantly reduced ST resolution observed in diabetic myocardial infarction patient ($\times 2 = 46.18$; $p < 0.001$)

Most commonly reported complications of streptokinase infusion were reported in table II. During hospital stay, among the notable complications, hypotension was observed in 22 (27.8%) and 32 (26.4%) patients, shock in 6 (7.6%) and 8 (6.6%), hemorrhagic manifestation was noted in 4 (5.1%) and 6 (4.9%) diabetic and non diabetic MI patients respectively.

Discussion

Intravenous streptokinase during acute myocardial infarction is a well recognized and effective treatment, which has beneficial effects on cardiovascular event related

mortality. Conceptually, therapeutic intervention for STEMI must minimize cell death by interrupting the ongoing process of infarction and attempt to reverse the ischemic metabolic derangement of still viable cells. The aim of thrombolysis in acute myocardial infarction is early and complete reperfusion. Incomplete or delayed reperfusion is associated with an increased risk of death and left ventricular dysfunction. The time to reperfusion and complete reperfusion remain the key determinants for fibrinolysis. ST segment recovery over serial ECG's in STEMI represents both reversal of ischemia and interruption of the infraction.

Among risk factors for coronary artery disease, diabetes is a major contributor, not only to the development of coronary artery disease but also to outcome following various manifestations of the disease.[25]

Some researchers have revealed similar angiographic[22] or electrographic[23] success in both diabetic and non diabetic patients, while other studies have shown that diabetics have less complete resolution of ST elevation than non diabetics.[24] To evaluate this issue, it was hypothesized, that diabetes might interfere within the effectiveness of intravenous thrombolysis, as estimated by angiographic or electrocardiographic criteria. The purpose of this study was to assess the thrombolytic effect of streptokinase in type 2 diabetic myocardial infarction patients by using 12 lead E.C.G and to compare with the non diabetic myocardial infarction patient in the same setting.

In a recent study ST resolution by thrombolytic versus primary coronary intervension[26] it was shown that ST segment resolution following thrombolytic therapy was complete 51.9%, partial 26.6% and failed resolution in 21.5% of acute myocardial infarction patients 90 min after the initiation of thrombolytic therapy.[27]. By using the same resolution criteria, in our study we observed the similar results in non diabetic myocardial infarction where 50.4% of patient showed complete resolution 31.4% parital resolution and 18.2% showed failed resolution. But in cases of diabetics STEMI, 19% of patients showed complete resolution, 12.7% partial resolution and 68.4% failed resolution.

In our study, more complete ST resolution was seen in non diabetic patients (50.4% vs 19.0%) while type 2 diabetic subjects presented with a significantly higher incidence of failed ST resolution non diabetic subjects (68.4% vs 18.2%). This significant change in ST resolution between diabetic and non diabetic group was similar with the study done by who showed significant difference between diabetic and non diabetic patient in relation to complete (19.0% vs 50.4% ; $p<0.001$) and incomplete (12.7% vs 31.4%; $p<0.001$) resolution.

In comparison between two groups, significantly reduced ST-resolution was observed in diabetic patients ($\div 2 = 46.18$, $p<0.001$). Our results are consistent with a published meta-analysis in which it was shown that type 2 diabetic subjects had less ST resolution after intravenous thrombolysis administration compared with non-diabetic subjects. Furthermore, certain altered properties of cellular component of blood[28] are also likely to enhance the potential of accumulating in the microcirculation of the heart, causing further danger by an oxygen radical-mediated inflammatory process.

Stress hyperglycaemia has a detrimental effect on thrombolytic outcome after acute myocardial infarction. Mortality may increase, especially in non diabetic patients. Diabetes can be differentiated from stress hyperglycaemia with certainly only after the acute phase of the infarction thus; any attempt

to identify undiagnosed diabetes in our study would have been biased because patients must survive the acute phase to be diagnosed.

Anaphylaxis and intracranial hemorrhage are the most serious complications of the streptokinase therapy. In their present study hypotension was the major complication in non-diabetic and diabetic patient (26.4% vs. 27.8%) while hemorrhage was least (4.9% vs. 5.1%)

In our study it was proved that reperfusion failed in a significant proportion of diabetic patient with STEMI in comparison with non-diabetic persons (68.4% vs. 18.2%). These finding reinforces the need for increased efforts to discover newer pharmacological agents to reduce failed reperfusion after streptokinase therapy in diabetic patients with myocardial infarction. To further improve outcome after myocardial infarction and thrombolysis among patients with diabetes, newer strategies such as peri-infarction metabolic control and primary angioplasty should be investigated.

Conclusion

The present results emphasize that, despite the established benefit of fibrinolytic therapy in acute myocardial infarction, a significant proportion of diabetic patients do not achieve complete reperfusion within 90 min of starting thrombolytic therapy. So, due attention is required for the better management of diabetic myocardial infarction patients. PCI may be the first choice of treatment in diabetic myocardial infarction patients if available.

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