

Impact of Diabetic Mellitus on the Effect of Streptokinase in Acute Myocardial Infarction Patients

Uddin MF¹, Hoque AKF²

Abstract

A prospective interventional study was carried out to compare the thrombolytic effect of streptokinase between diabetic and non-diabetic myocardial infarction patients. Out of 187 study subjects with acute ST segment elevation myocardial infarction (STEMI), admitted at coronary care unit, 126 patients were non-diabetic and 61 patients were diabetic. Streptokinase was administered to all patients. Resolution (reduction) of elevated ST segment was evaluated after 90 min of streptokinase administration. Successful reperfusion (=70% ST-resolution) was significantly higher in non-diabetic than diabetic ($p < 0.001$), while failed reperfusion (<30% ST resolution) was significantly higher in diabetic patients ($p < 0.001$). It may be concluded that diabetes mellitus might affect the thrombolytic outcome of acute myocardial infarction patients with diabetes mellitus.

Introduction

Acute myocardial infarction may be considered as a potential epidemic for mankind¹. Incidence of coronary disease is increasing in Bangladesh². Death rates from coronary heart disease in UK are among the highest in the world but are falling now³. 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 Europeans⁴.

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 occlusion⁵.

Among patients with an acute myocardial infarction, 10-25% has diabetes⁶. Even when promptly receiving thrombolytics the outcome in diabetic subjects is still worse than non-diabetics, manifesting impaired post-thrombolysis left ventricular function and prognosis⁷.

The aim of thrombolysis in acute myocardial infarction is early and complete myocardial reperfusion. Incomplete or failed reperfusion is associated with an increased risk of death and left ventricular dysfunction. 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 1958⁸. However, newer fibrinolytic agents are equivalent but not superior to older non-selective agents⁹.

Use of streptokinase in patients with acute myocardial infarction is considered up to 12 hours after the onset of chest pain¹⁰. 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 electrocardiogram⁷. 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 fibrinolytics¹³.

Mortality after acute myocardial infarction in patients with diabetes is about twice that of nondiabetic patients¹⁴. 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 diabetes¹⁵. 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. In this study, we evaluated the impact of type 2 diabetes in intravenous thrombolysis effectiveness by using a 12-lead ECG.

1. Corresponding Author: Dr. Md. Faruque Uddin, MBBS, MD
Clinical & interventional Cardiologist
Associate Professor & Head of the Department of Cardiology
North East Medical College, Sylhet
2. Dr. A.K Fazlul Hoque, MBBS, MD
Clinical & interventional Cardiologist
Associate Professor, Cardiology
North East Medical College, Sylhet.

Material and Methods

This prospective interventional study was carried out during the period of July 2008 to June 2010. The patients, who were admitted in coronary care unit at North East Medical College, Sylhet with the diagnosis of ST elevation myocardial infarction, were taken as the study subjects. 187 patients with acute myocardial infarction were selected, 126 patients were non-diabetic and 61 were diabetic.

Inclusion criteria were- patients with STEMI came within 12 hours of chest pain, known diabetic or established during hospital stay by repeated blood glucose estimation. Exclusion criteria were – late presentation, after 12 hours of chest pain, type 1 diabetes, IGT, history of previous myocardial infarction.

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. Fasting plasma glucose was recorded from all patients, in the morning of 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' wave¹⁶.

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 resolution) towards baseline within 90 minute after streptokinase infusion has been shown to be a useful predictor of successful reperfusion¹⁷. The ST-segment elevation resolution stratified by¹⁸, into 3 categories: a) complete ST resolution ($\geq 70\%$ 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).

Twelve-lead ECG was recorded immediately before start of thrombolytic therapy and at 90 minutes thereafter from the patient with ST elevation myocardial infarction.

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 percentage¹⁸. Complete ST resolution ($\geq 70\%$ 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, partial ST-resolution ($< 70\%$ to 30%) is related to impairment of reperfusion at the myocardial level reflecting the unpredictable effect of streptokinase^{19, 20}.

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 (χ^2) were done where applicable.

Results

Grouping of study subjects, sex distribution, socio-economic and risk factors characteristics were presented in Table-I. Patients of both group were matched in respect to age, sex, socio-economic status and associated risk factors.

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

Variables	Non-diabetic (n=126)	Diabetic (n=61)
Age (mean \pm SD) year	48.5 \pm 9.1	51.2 \pm 9.7
Number of male	115 (91.3%)	56 (91.8%)
Number of female	11 (8.7%)	5 (8.2%)
Positive smoking history	97 (77.0%)	45 (73.8%)
Sedentary life style	67 (53.2%)	37 (60.7%)
Family history of coronary artery disease	55 (43.6%)	26 (42.6%)
BMI (mean \pm SD) kg/m ²	27.3 \pm 1.2	27.5 \pm 1.1
Time of thrombosis after admission (mean \pm SD) hour	5.68 \pm 1.5	4.87 \pm 2.3
History of hypertension	73 (57.9%)	36 (59.0%)

Table II shows comparison of ST-resolution at 90 min after streptokinase between non-diabetic and diabetic myocardial infarction patients where complete ST-resolution occurred in 61 (48.4%) and 12 (19.6%) patients respectively. The incidence of partial ST-resolution in non-diabetic and diabetic patients was 40 (31.7%) and 8 (13.1%) where 25 patients in non-diabetic and 41 patients in diabetic patients showed failed ST resolution. Chi-square (χ^2) test was done to assess the influence of diabetes on the efficacy of streptokinase, by evaluating difference of ST-resolution between diabetic and non-diabetic subjects. There was significantly reduced ST-resolution observed in diabetic myocardial infarction patient ($\chi^2 = 40.69$; $p < 0.001$).

Table II: Comparison of ST resolution between non-diabetic and diabetic infarctions patients

Group	Number of patients showing ST resolution at 90 min after streptokinase			Total	Chi volume	p
	Complete	Partial	Failed			
Non-diabetic	61 (48.4 %)	40 (31.7 %)	25 (19. %)	126	40.69	<0.001
Diabetic	12 (19.7 %)	8 (13.1 %)	41 (67.2 %)	61		
Total	73	48	66	187		

Most commonly reported complications of streptokinase infusion were reported in Table III. During hospital stay, among the notable complications, hypotension was observed in 34 (27.0%) and 18 (29.6%) patients, shock in 8 (8.7%) and 7 (11.4%), hemorrhagic manifestation was noted in 6 (4.8%) and 5 (8.2%) non-diabetic and diabetic myocardial infarction patients respectively.

Table III: Streptokinase infusion related complications in non-diabetic and diabetic myocardial infarction patients

Complications	Non-diabetic patients (n=126)	Diabetic patients (n=61)	p value
Hypertension	34(27.0%)	18(29.6%)	0.319
Shock	8 (8.7%)	7 (11.5%)	0.268
Hemorrhagic manifestation	6 (4.8%)	5 (8.2 %)	0.311

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 infarction.

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 disease²¹.

Several studies have reported similar angiographic^{22,14} or ECG^{6,23} success in both type 2 diabetic and non-diabetic subjects, while others have shown that the diabetics have less complete resolution of ST elevation than the non-diabetics^{22,7}. To evaluate this issue, it has been hypothesized that type 2 diabetes might interfere with intravenous thrombolysis effectiveness, as estimated by angiographic or ECG 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 ECG and to compare with the non-diabetic myocardial infarction patient in the same setting.

In a recent study of ST-segment resolution by thrombolytic, showed the resolution of ST-segment by thrombolytic are as follows: complete 51.9%, partial 26.6% and failed resolution in 21.5% acute myocardial infarction patients after 90 min of initiation of fibrinolytic therapy²⁴. By using the same resolution criteria, in our study we observed the similar results in non-diabetic myocardial infarction where 48.4% patients showed complete resolution, 31.7% patient's partial resolution and 19.8% showed failed resolution. But in case of diabetic myocardial infarction, 19.7% patients showed complete resolution, 13.1% partial resolution and 67.2% showed failed resolution.

In our study, more 'complete ST-resolution' was seen in non-diabetic patient (48.4% vs. 19.7%; Z=4.25; p<0.001) whereas type 2 diabetic subjects were presented with significantly higher incidence of failed ST-resolution than non-diabetic subjects (67.2% vs. 19.8%; Z=6.79; p<0.001). This significant change in ST-resolution between non-diabetic and diabetic group was similar with the study done by⁷ who showed significant difference between diabetic and non-diabetic patient in relation to complete (34.1% vs. 68.2%; p<0.001) and incomplete (65.9% vs. 31.8%; p<0.001) resolution.

In comparison between two groups, significantly reduced ST-resolution was observed in diabetic patients ($\div 2 = 40.69$, 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 subjects²². Furthermore, certain altered properties of cellular component of blood²⁵ 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 hyperglycemia 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 hyperglycemia with certainty 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 the present study hypotension was the major complication in non-diabetic and diabetic patient (27.0% vs. 29.6%) while hemorrhage was least (4.8% vs. 8.2%).

In our study it was proved that reperfusion failed in a significant proportion of diabetic patient with STEMI in comparison with non-diabetic persons (67.2% vs. 19.8%). 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.

In 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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