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COMPARISON OF THE EFFICACY AND SAFETY OF THROMBOLYTIC THERAPY FOR ST-ELEVATION MYOCARDIAL INFARCTION IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS

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ABSTRACT

Objective: This study compared the efficacy and safety of streptokinase as thrombolytic agent for ST-elevation myocardial infarction (STEMI) in patients with and without diabetes mellitus.

Methodology: This prospective interventional study was carried out in the department of Cardiology, Postgraduate Medical Institute Govt. Lady Reading Hospital Peshawar. A total of 444 patients admitted to coronary care unit with STEMI and eligible for thrombolytic therapy (no contraindications per AHA/ACC guidelines) were studied from December 2009 to December 2010. Among these half of patients were diabetic while rests were non-diabetic. Streptokinase was administered to all patients. Resolution (reduction) of elevated ST segment was evaluated after 90 min of streptokinase administration. Comlications of streptokinase infusion including hypotension, shock and hemorrhage was noted.

Results: Failed reperfusion (<30% ST resolution) was significantly higher in diabetic as compared to non-diabetic patients (21.6% vs. 9.5%; p<0.0003) while successful reperfusion (⩾70% ST-resolution) was significantly higher in non-diabetic than diabetic patients (66.7% vs. 49.1%; p<0.0001). Complication rates between the two groups were statistically similar. Hypotension occurred in 45 (20.3%) and 51 (23%); p=0.458 patients in non-diabetic and diabetic group respectively while shock occurred in 10 (4.5%) and 13 (5.9%); p= 0.506 and hemorrhagic manifestations in 13 (5.9%) and 10 (4.5%); p=0.294 patients respectively.

Conclusion: The outcome of thrombolytic therapy is adversely affected by Diabetes mellitus in patients with ST-elevation myocardial infarction. Secondly the risk of hazards associated with thrombolytic therapy is same in both diabetic and non-diabetic patients.

Key Words: Diabetes mellitus, Thrombolytic Outcome, ST-elevation Myocardial Infarction

INTRODUCTION

Myocardial infarction (MI) is the leading cause of death worldwide. Its annual incidence in the United States is estimated to be 600 000 new and 320 000 recurrent attacks. In 2004, AMI resulted in 695000 hospital stays and $31 billion in hospital charges.[1, 2] In Pakistan it is estimated that one in five middle-aged adults may have underlying coronary artery disease (CAD).[3] Similarly Diabetes mellitus is also an epidemic disease. It is estimated that the total number of people with diabetes will rise from 171 million in 2000 to 366 million by 2030. Its worldwide prevalence is expected to double by the year 2030. Pakistan is also facing heavy burden of diabetes with estimated prevalence of 12%.It has affected approximately 6.9 million people in this country and predicted to affect 11.5 million people by 2025. World Health Organization (WHO) has ranked Pakistan 6th on diabetes prevalence list .[4, 5]

Diabetes is a dyslipidemic disease and increases the rate of atherosclerotic progression of vascular occlusion.[6] Among patients with an acute myocardial infarction, 10-25% has diabetes.[7]Even when promptly receiving thrombolytics, the outcome in diabetic subjects is still worse than non-diabetics, manifesting as impaired post-thrombolysis left ventricular function and prognosis.[8] 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) non-selective fibrinolytic agent (streptokinase, anistreplase and 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.[9] However, newer fibrinolytic agents are equivalent but not superior to older non-selective agents.[10]

Use of streptokinase in patients with AMI is considered up to 12 hours after the onset of chest pain. But the 1st hour is considered golden for thrombolytic therapy.[11] The outcome of AMI 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.[8] 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.[12] ST segment resolution within 90 min is a simple measure of assessing reperfusion in patients receiving fibrinolytics.[13]

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

A number of studies conducted in Europe and United States have demonstrated that thrombolytic treatment for ST-elevation myocardial infarction is less successful in diabetic as compared to non-diabetic patients.[8] However there are very few studies which look at the outcome of thrombolytic therapy for STEMI in diabetic patients in our community. In this study, we evaluated the impact of type 2 diabetes on thrombolytic effectiveness by using a 12-lead ECG.

METHODOLOGY

This prospective interventional study was conducted in the department of Cardiology, Postgraduate Medical Institute Govt. Lady Reading Hospital Peshawar from December 2009 to December 2010 for a total period of one year. The estimated sample size was 127patients in each group using 67.2% proportion of failed thrombolysis in diabetic and 19.8% proportion in non- diabetic with 90% power, 10% significance level and 15% margin of error using Fleiss sample size estimating formula.[6] But a larger sample of 444 patients was taken and it was equally divided between two groups i.e. 222 in each group. Purposive non probability sampling technique was used. Inclusion criteria were patients with STEMI came within 12 hours of chest pain and eligible for thrombolytic therapy (no contraindications per AHA/ACC guidelines). It included both genders of patients with age ranged from thirty to eighty years. Exclusion criteria were late presentation after 12 hours of chest pain, type1 diabetes, history of previous myocardial infarction, previous use of streptokinase, past coronary bypass surgery (CABG), premature discontinuation of intravenous thrombolytics due to complications and patients with new or old left bundle branch block on ECG.

The hospital ethical committee approved the study protocol and informed consent was obtained from all participants. Streptokinase (streptase) was given to each patient through infusion pump at a dose of 1.5 million units, diluted in 100 ml of normal saline, in 1 hour. Chewed aspirin in a dose of 160–325 mg and clopidogrel 300 mg was administered upon admission. Unfractioned heparin was given as appropriate in a bolus of 60 units/kg (up to 5,000) upon admission, followed by intravenous infusion of 12 units /kg /h titrated to a therapeutic activated partial thromboplastin time. Heparin was continued in uncomplicated case subjects for 48 h.Twelve-leads ECG was recorded immediately before start of thrombolytic therapy and at 90 minutes thereafter. Thrombolytic success or failure was assessed as defined in the operational definitions. 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 and hemorrhagic manifestations (like Intra cranial, hemitemesis or melana, frank hematuria, nasal cavity and intravenous access site) following streptokinase were noted.

ECG criteria were used to asses' thrombolytic success or failure. Elevation of ST segment occurs during AMI, which returns to the is-electric 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 reperfusion.

Schroder et al. stratified the ST-segment elevation resolution into 3 categories: a) complete ST resolution ($\geqslant$ 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).[15] Twelve-lead ECG was recorded immediately before start of thrombolytic therapy and at 90 minutes thereafter from the patient with STEMI. The sum of ST-segment elevation was measured by hand held caliper at 80 ms (two small squares) beyond the 'J' point in leads I, aVL, V_1 to V_6 for anterior, leads II, III, aVF for inferior and lead V_1 to V_4 for anteroseptal infarction.[16] 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 percentage.[15]

All this data were recorded on a proforma. Confounding variables mentioned in the exclusion criteria were controlled. Bias in the study was controlled by following strict inclusion criteria for patient's selection, use of the same brand of streptokinase for all patients, measurable operational definitions for assessing success or failure and adverse outcome of thrombolytics.

Statistical analysis was performed using statistical package for social sciences (SPSS) version 16. Numerical variables were presented as mean±SD. Categorical variables were presented as frequencies and percentages. Comparison between two groups was performed by using student-t test for numerical variables and Chi-Square test for categorical variables. P-value $\leqslant$ 0.05 was considered significant. Results were presented as tables.

RESULTS

Patient Characteristics: Among 444 patients with STEMI, half of patients were diabetic while rests were non-diabetic. Patient baseline characteristics are shown in Table 1. Most of the baseline characteristics were statistically similar between the two groups. However diabetic patients had more hypertension as compared to non-diabetic patients.

Thrombolytic outcomes: Failed reperfusion (<30% ST resolution) was significantly higher in diabetic as compared to non-diabetic patients 21.6%V 9.5% (p<0.0003) while successful reperfusion ($\geqslant$ 70% ST-resolution) was

Table 1: Baseline Characteristics of Non-diabetic and Diabetic Patients with ST-Elevation Myocardial Infarction

Variable	Non-diabetic Patients (n=222)	Diabetic Patients (n=222)	P-value
Age (mean ± SD) years	56.42±10.30	57.19±9.95	0.401
Male (%)	135(60.8)	123(55.4)	0.216
Female (%)	87(39.2)	99(44.6)	0.214
Smoking history	90(40.5)	84(37.8)	0.482
Hypertension	68(30.6)	124(55.9)	0.01
Family history of CAD	78(35.1)	85(38.3)	0.078
Dyslipidemia	101(45.7)	108(48.4)	0.564
Symptoms to thrombolysis time (mean ± SD) hour	3.48±1.75	3.79±1.98	.077

Table 2: Comparison of ST Resolution between Non-diabetic and Diabetic Patients with ST-Elevation Myocardial Infarction

ST-Resolution	Non-diabetic Patients (n=222)	Diabetic Patients (n=222)	P-value
Complete	148(66.7)	109(49.1)	0.0001
Partial	53(23.9)	65(29.3)	0.178
Failed	21(9.5)	48(21.6)	0.0003

Table 3: Streptokinase Infusion Related Complications in Non-diabetic and Diabetic Patients with ST-Elevation Myocardial Infarction

Complications	Non-diabetic Patients (n=222)	Diabetic Patients (n=222)	P-value
Hypotension	45(20.3)	51(23)	0.458
Shock	10(4.5)	13(5.9)	0.506
Hemorrhage	13(5.9)	10(4.5)	0.294

significantly higher in non-diabetic than diabetic patients 66.7%V 49.1 %(p<0.0001). Partial reperfusion was also higher in diabetics as compared to non-diabetics, however it did not reach statistical significance 29.3%V23.9% P= 0.178 . These were presented in Table 2.

Complications associated with streptokinase administration were statistically similar between two groups. These are presented in Table 3. Hypotension occurred in 45 (20.3%) and 51 (23%) P=0.458 patients in non-diabetic and diabetic group respectively while shock occurred in 10 (4.5%) and 13 (5.9%) P=0.506 and hemorrhagic manifestation in 13 (5.9%) and 10 (4.5%) P= 0.294 patients respectively.

DISCUSSION

Thrombolytic therapy for STEMI is a well recognized and effective treatment. 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 STEMI 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 patients represents both reversal of ischemia and interruption of the infarction.[17]

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.[17]

Several studies have reported similar angiographic or ECG success in both diabetic and non-diabetic subjects, while others have shown that the diabetics have less complete resolution of ST elevation than the non-diabetics.[13,18] A recent comparative study of ST-segment resolution by thrombolytic versus primary coronary intervention (PCI) showed the resolution of ST-segment by thrombolytics are as follows: complete 51.9%, partial 26.6% and failed resolution in 21.5% STEMI patients after 90 min of initiation of fibrinolytic therapy.[19] By using the same resolution criteria, in our study we observed the similar results in non-diabetic myocardial infarction where 66.7% patients showed complete resolution, 23.9% patient's partial resolution and 9.5% showed failed resolution. But in case of diabetic myocardial infarction 49.1% patients showed complete resolution, 29.3% partial resolution and 21.6% showed failed resolution.

In this study, more complete ST-resolution was observed in non-diabetic as compare to diabetic patients (66.7% vs. 49.1% p<0.0001) whereas incidence of failed ST-resolution was significantly higher in diabetic than non-diabetic subjects (21.6 % vs. 9.5%; p<0.0003). This significant difference in ST-resolution between non-diabetic and diabetic group was similar with the study done by Zairis et al.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.[20] Our results are also consistent with a published meta-analysis in which it was shown that type 2

diabetic subjects had less ST resolution after intravenous thrombolytics administration compared to non-diabetic subjects.[13]

Anaphylaxis and intracranial hemorrhage are the most serious complications of the streptokinase therapy.[6] In the present study hypotension was the most common complication in both study groups while hemorrhage was the least. There was no difference in complication rates between the two groups statistically. This suggests that thrombolytic therapy is as safe in diabetic as in non-diabetic patients.

In our study it was proved that reperfusion failed in a significant proportion of diabetic patient with STEMI in comparison to non-diabetic persons. These finding reinforces the need for increased efforts to discover newer pharmacological agents to reduce failed reperfusion 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, 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 myocardial infarction in diabetic patients. Further therapies and strategies directed towards the many abnormalities that are associated with diabetes, such as endothelial dysfunction, dysglycemia and coagulation and fibrinolytic disturbances are needed to be explored.

CONCLUSION

The results of this study suggest that a significant proportion of diabetic patients do not achieve complete reperfusion within 90 min of starting thrombolytic therapy. Secondly diabetic and non- diabetic patients have similar risk of complications from thrombolytic therapy.

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REFERENCES

1. Khan S, Kundi A, Sharieff S. Prevalence of right ventricular myocardial infarction in patients with acute inferior wall myocardial infarction. Int J Clin Pract 2004;58:354-7.
2. Russo CA, Andrews RM. The national hospital bill: the most expensive condition by payer, 2004 [Online]. 2004 [cited on 2009 Sep 09]. Available from URL: http://www.ncbi.nlm.nih.gov/books/NBK63505.
3. Jafar TH, Jafary FH, Jessani S, Chaturvedi N. Heart disease epidemic in Pakistan: women and men at equal risk. Am Heart J 2005;150:221-6.
4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
5. Imperatore G, Cadwell BL, Geiss L, Saadinne JB, Williams DE, Ford ES, et al. Thirty-year trends in cardiovascular risk factor levels among US adults with diabetes: National Health and Nutrition Examination Surveys, 1971–2000. Am J Epidemiol 2004;160:531-9.
6. Chowdhury AR, Hossain M, Dey SR, Akhtaruzzaman AKM, Islam N. A comparative study on the effect of streptokinase between diabetic and non-diabetic myocardial infarction patients. Bangladesh J Pharmacol 2008;3:1-7.
7. Mak KH, Moliterno DJ, Granger CB, Miller DP, White HD, Wilcox HD, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. J Am Coll Cardiol 1997;30:171-9.
8. Zairis MN, Lyrus AG, Makrygiannis SS, Psarogianni PK, Adamopoulou EN, Handanis SM. Type 2 diabetes and intravenous thrombolysis outcome in the setting of ST elevation myocardial infarction. Diabetes Care 2004;27:967-71.
9. Hermentin P, Cuesta-Linker T, Weisse J, Schmidt KH, Knorst M, Scheld M, et al. Comparative analysis of the activity and content of different streptokinase preparations. Eur Heart J 2005;26:933-40.
10. Sabatine MS, Cannon CP, Gibson CM, Lopez-sendon JL, Montalescot G, Theroux P, et al. Addition of clopidegrol to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. New Engl J Med 2005;352:1179- 89.
11. Maxwell S. Emergency management of acute myocardial infarction. Br J Clin Pharmacol 1999;48:284-8.
12. Van t'Hof AW, Liem A, de Boer MJ, Zijlstra F. Clinical value of 12 lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle Myocardial Infarction Study Group. Lancet 1997;350: 615-9.
13. Angeja BG, DeLemos J, Murphy SA, Marble SJ, Antman EM, Cannon CP, et al. Thrombolysis in myocardial

infarction: impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. Am Heart J 2002;144:649-56.

14. Woodfield SL, Lundergan CF, Reiner JS, Greenhouse SW, Thompson MA, Rohrbeck SC, et al. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: The GUSTO-I experience. J Am Coll Cardiol 1996;28: 1661-9.
15. Schroder R, Dissmann R, Bruggemann T, Wegscheider K, Linderer T, Tebbe U, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994;24:384-91.
16. Purcell IF, Newell N, Farrer M. Change in ST segment elevation 60 minutes after thrombolytic initiation predicts clinical outcome as accurately as later electrocardiographic changes. Heart 1997;78:465-71.
17. Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Ryden L, et al. Diabetes mellitus: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. J Am Coll Cardiol 2004;43:585-91.
18. Ishihara M, Sato H, Kawagoue T, Shimatani Y, Kurisu S, Nishioka K, et al. Impact of diabetes mellitus on long-term survival after acute myocardial infarction in patients with single vessel disease. Heart 2001;86:133-8.
19. Thiele H, Engelmann L, Elsner K, Kappl MJ, Storch WH, Rahimi K, et al. Comparison of pre-hospital combination fibrinolysis plus facilitated percutaneous coronary intervention in acute myocardial infarction. Eur Heart J 2005;26:1956-63.
20. Zairis MN, Makrygiannis SS, Papadaki OA, Lyras AG, Kouzanidis JP, Ampartzidou OS, et al. Diabetes and ST elevation myocardial infarction. Diabetes Care 2002;25:1890-1.