COMPARISON OF THROMBOLYTIC SUCCESS IN PATIENTS UNDERGOING REPERFUSION THERAPY WITH STREPTOKINASE FOR ST ELEVATION MYOCARDIAL INFARCTION, IN TERMS OF CULPRIT ARTERY PATENCY IN DIABETICS VS NON DIABETICS

Zain Mehmood Butt[a*], Zille Huma[b], Ahmed Muqeet[a], Gul Shan Ahmad[c], Sohail Rashid[a], Salman Ahmad[c]

[a]Jinnah Hospital Lahore, Lahore. [b]National Institute of Cardiovascular Diseases, Karachi. [c]Punjab Institute of Cardiology, Lahore

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ABSTRACT:

BACKGROUND: *Myocardial infarction (MI) secondary to the atherosclerosis of coronary arteries remains the major reason of morbidity and mortality worldwide. Thrombolysis in acute MI is prompt and optimal myocardial reperfusion while partial or failed reperfusion is linked with increased risk of complications and adverse outcomes.*

AIMS & OBJECTIVE: *Comparison of thrombolytic success in patients undergoing reperfusion therapy with streptokinase (SK) for ST elevation myocardial infarction, in terms of culprit artery patency in diabetics vs non diabetics.*

MATERIAL & METHODS: *This descriptive cross-sectional study was carried-out in cardiology department, Jinnah Hospital Lahore from 01-07-2017 to 31-12-2017. Total 200 patients with STEMI fulfilling the inclusion criteria were approached and enrolled in the study after obtaining an informed consent. Blood sugar level was assessed for every patient at first medical contact. A baseline twelve-lead ECG done before the administration of SK and culprit artery recorded (as per operational definition). Patients were administered SK in a dose of 1.5 million IU over an hour with constant monitoring. Coronary angiogram was done 24 hours post thrombolysis to assess the patency of culprit artery. Frequency of the culprit artery patency was compared between diabetics and non-diabetics by using chi square test considering the p value <0.05 as statistically significant.*

RESULTS: *Mean age of study population was 46.74 + 9.71 years. The mean blood sugar random (BSR) was 173.62 + 61.08 mg/dL. Study included 56% (n=112) male patients and 44% (n=88) female patients. 23% (n=46) were diabetics among them. The percentage of culprit artery patency in diabetic patients was lower compared to non-diabetics patients (43.5% vs 74.0%, p-value = 0.00). In more than 40 years age group, the culprit artery patency was significantly lower in diabetics compared to non-diabetics (40.5% vs 74.3%, p =0.000).*

CONCLUSION: *Thrombolytic success in terms of culprit artery patency was lower in diabetic vs non-diabetic patients and association was observed in both genders. However, in younger patients (<40 years) such association was not found.*

KEY WORDS: *Myocardial Infarction, Diabetes, Reperfusion Therapy, Culprit Artery Patency.*

Correspondence : Zain Mehmood Butt, Jinnah Hospital Lahore. Email: drzainbutt@gmail.com

Author's Contribution: ZMB: Conducted study. ZH: Data analysis, interpretation, study design & drafting. AM: Literature search, Data collection and analysis. GA: Drafting of work & revised it, Data collection.SR: Data collection, questionnaire design, drafting. SA: Drafting & data collection, data interpretation

INTRODUCTION:

Atherosclerotic coronary artery disease, especially myocardial infarction remains the major reason of mortality worldwide, with over 80% of deaths being reported from low- and middle-income countries as cited in WHO report from 2011[1].

The foundation of STEMI care includes fibrinolysis, Primary PCI and pharmaco-invasive strategies, however, due to significant cost burden and non-availability of primary PCI facilities, fibrinolytic therapy has been established the preferred strategy in majority of the developing countries including Pakistan. When used in timely fashion (within 6 hours of presentation), even the first generation thrombolytic agent i.e Streptokinase has been associated with significant reduction in mortality[2] and is still being used effectively for 400,000-500,000 patients per year, world wide[3]. The clinical benefit is however less pronounced in diabetic cohorts. Despite being the corner stone of treatment for STEMI patients, reperfusion strategies including thrombolysis, have proven less effective in diabetic patients as compared to non diabetics[4].

Multiple studies have confirmed that the presence of diabetes in ACS setting confers worse prognosis. A comparative study carried out by Chowdhury et al.[5], on STEMI patients treated with Streptokinase has documented significantly higher incidence of failed reperfusion in diabetic patients vs non-diabetic group being 67.2% vs 19.8 % respectively. Subgroup analysis of patients with diabetes with ST-segment elevation MI (STEMI) in GUSTO-1trial[6] demonstrated significantly higher all-cause mortality at 30 days compared with patients without diabetes (10.5% vs 6.2%). Another study performed recently by Hathi V et al. [7], reported a very high mortality of 23.52% in diabetic cohort vs zero mortality in non-diabetics. Failure of symptom resolution and other complications like arrhythmia and heart failure were also more prevalent in diabetic population.

Just like clinical parameters, impaired blood glucose level has also shown negative impact on various ECG and angiographic findings. Based on multiple studies[8,9,10] ECG evaluation of STEMI patients treated with thrombolysis has shown that non-resolution of ST elevation in acute MI occurred more frequently in diabetics as compared with non diabetics.Iwakura et al[11] have studied the impact of hyperglycaemia on myocardial contrast echocardiography (MCE) after successful reperfusion of 146 patient with STEMI. Based on their assessment, blood glucose level on admission was significantly higher in patients who exhibited no reflow phenomenon on MCE. Ehl et al[12] studied that diabetic patients revealed a lower LVEF than non-diabetic patients regardless of CAD extent and recommended that this difference was linked with worse CV mortality in diabetic patients.

Elevated blood glucose level at admission has also been documented as independent predictor of impaired microvascular flow in patients undergoing primary PCI. In 308 patients with STEMI subjected to primary PCI, incidence of TIMI myocardial perfusion grade (TMPG) 0 - 1 grade was significantly higher in patients with hyperglycaemia as compared to those with normal blood glucose levels (30.9% and 29.0% vs 17.3%, $P < 0.05$) and this was further translated into incomplete ST resolution following revascularization[13]. Impairment of epicardial flow in STEMI patients is also strongly linked with hyperglycaemia. According to a more recent prospective study of 460 STEMI patients planned to undergo primary PCI, impairment of pre-procedural TIMI flow was documented more frequently in patients with hyperglycaemia (12% vs 28%, $p<0.001$) [14].

STEMI patients who fail to achieve optimal TIMI flow in culprit artery following reperfusion, have been reported to have increased incidence of major adverse events. Lincoff et al[15] carried out prospective analysis of TIMI flow in 1229 patients undergoing fibrinolysis for acute STEMI, followed by angiographic assessment of infarct related artery after 90 minutes. It demonstrated a significant association of increasing mortality with lower TIMI flow (4.3%, 6.1%, and 10.1% with TIMI 3, 2, and 0/1 flow, respectively, $p = 0.002$). Patients with poor TIMI flow also showed significantly increased incidence of congestive heart failure as well as recurrent ischaemia in comparison with those

with TIMI III flow of culprit artery (26% vs 19% for heart failure , p = 0.03; 23% vs 17% for recurrent ischemia, p = 0.05).

Both diabetes and poor TIMI flow of culprit artery are therefore major determinants of adverse outcome in STEMI patients. Although there is strong evidence available regarding the association of diabetes with coronary microvascular dysfunction[16,17] there is still uncertainty about the impact of diabetes on epicardial flow in STEMI patients following reperfusion. This study was therefore conducted to see the comparison of thrombolytic success in patients undergoing reperfusion therapy with streptokinase for ST elevation myocardial infarction, in terms of culprit artery patency in diabetics vs non diabetics.

MATERIAL AND METHODS:

This descriptive, cross-sectional study was carried out at Cardiology Department of Jinnah Hospital, Lahore from 01-07-2017 to 31-12-2017. A total number of 200 patients with acute STEMI were included by using non-probability purposive sampling technique. Sample size was calculated with 95% confidence level, 6% margin of error and taking expected percentage diabetes mellitus i.e; 20.3% in patients presenting with Acute STEMI.

Consecutive patients of both male and female gender between 20-60 years of age presenting with acute STEMI were selected. Patients having history of prior MI or previous percutaneous or surgical revascularization, late presentation more than 6 hours after the pain onset, having active bleeding / Procoagulant disorders determined on history and examination, pre-existing left bundle branch block on ECG, having any of the contraindications to thrombolytic therapy and those not willing for or having any contraindication to coronary angiography were excluded from the study. Informed consent was taken from all patients. Information regarding their demographic data was noted in the proforma. BSR was done on 2 ml venous blood to find diabetes (as per operational definition).

A baseline twelve-lead ECG was done before the administration of SK and culprit artery was recorded based on ECG findings. Patients were administered SK in a dose of 1.5 million IU over an hour with continuous hemodynamic and ECG monitoring. Coronary angiogram was performed 24 hours after thrombolysis to check patency of culprit artery. Results were noted in the proforma and confidentiality of the data was ensured.

DATA ANALYSIS:

Statistical analysis of data was performed by using SPSS version 17.0. Numerical variable i.e. age was described as mean + SD (standard deviation). Qualitative variables like gender and patency of culprit artery were described in the form of frequency and percentages. The frequency of culprit artery patency was compared between diabetic and non diabetic using Chi square test as test of significance. P-value < 0.05 was used as statistically significant. Effect modifiers like age and gender were addressed through stratification. Post-stratification chi-square test was applied.

RESULTS:

Mean age of study population was 46.74 + 9.71 years. 27.0% were less than 40 years and 73.0% were more than 40 years. (Table.1). The mean BSR was 173.62 + 61.08 mg/dL. Study included 56% (n=112) male patients and 44% (n=88) female patients (Figure=1) and 23% (n=46)of the study population was diabetic (Figure=2). The frequency of left anterior descending (LAD) as culprit vessel was observed in 48%, right coronary artery (RCA) in 32% and left circumflex artery (LCx) in 20% of cases. (Figure =3)

The frequency of culprit artery patency was67% (n=134) in patients undergoing reperfusion therapy with streptokinase. The percentage of culprit artery patency in diabetic cohort was 43.5% (n=20) while it was noted as 74.0% (n=114) in non-diabetic subgroup. The frequency of patency was therefore lower in diabetics compared to non-diabetics patients (43.5% vs 74.0%) and the

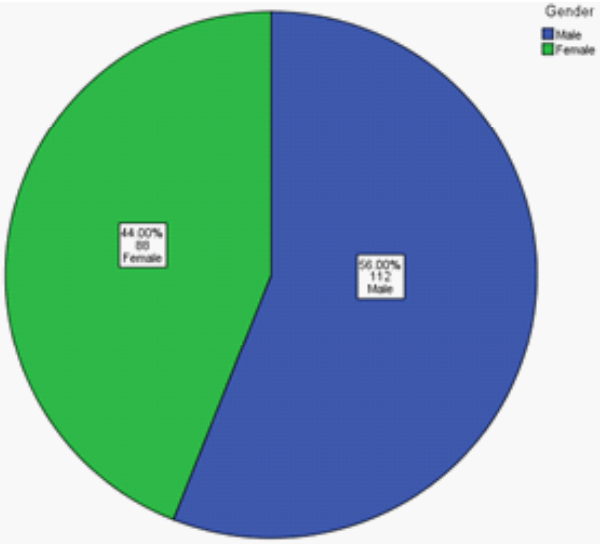

Figure.1 Distribution of Gender (n = 200)

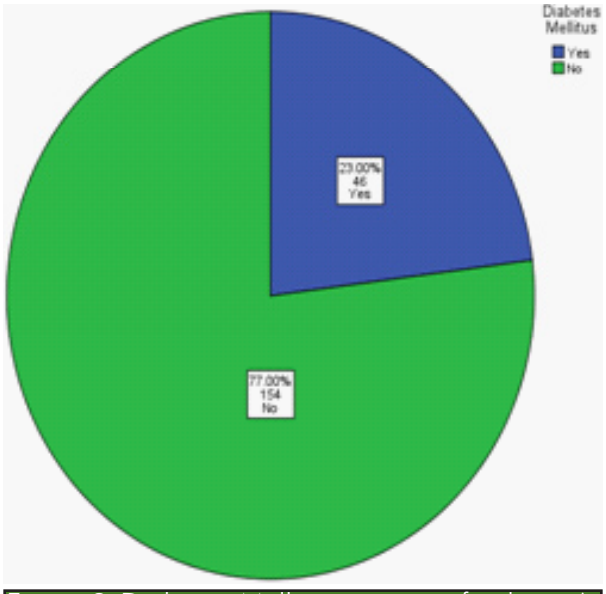

Figure:2 Diabetes Mellitus among of subjects(n = 200)

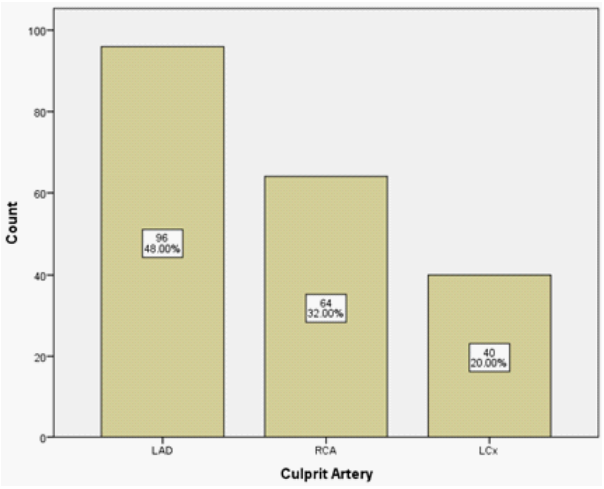

Figure: 3 Distribution of Culprit Artery(n = 200)

Table no: 1 Age of subjects

Age	Frequency	Percentage
< 40 years	54	27.0
> 40 years	146	73.0
Total	200	100.0
Mean= 46.74 SD = 9.714 Min= 20 Max= 60		

Table No: 2 Comparison of Patency in Diabetic and Non-Diabetic Patients(n = 200)

Patency	Diabetic		Total	Chi-square P value
	Yes	No		
Yes	20	114	134	X2 =14.949 P =.000
	43.5%	74.0%	67.0%	
No	26	40	66	
	56.5%	26.0%	33.0%	
Total	46	154	200	
	100.0%	100.0%	100.0%	

difference was statistically significant (p-value = 0.000). (Table.2)

Stratification of patency among diabetic mellitus was done for age and gender. In less than 40 years age group, the culprit artery patency was documented as 55.6% in diabetics and 73.3% in non-diabetics and was found to be statistically non-significant (p=0.286). In more than 40 years age group, the culprit artery patency was present in 40.5% of diabetic and 74.3% of non-diabetic subjects and was noted as statistically significant (p =0.000). (Table.3)

In males, culprit artery patency was found in 43.3% of diabetics and 70.0% of non-diabetic subjects and was statistically significant (p= 0.005). In females, culprit artery patency was recorded in 43.8% of diabetic patients and 76.4% of non-diabetic subjects and was statistically significant (p= 0.010) (Table 3).

DISCUSSION:

This single center descriptive study determined the frequency of diabetes mellitus in patients presenting with Acute STEMI at our non-PCI capable facility and revealed that the frequency

Table 3: Stratification with respect to age and gender (n = 200)

		Patency	Diabetes Mellitus		Total	Chi-square P value
			Yes	No		
Age	< 40 years	Yes	5	33	38	X^2 =1.137 P =0.286
			55.6%	73.3%	70.4%	
		No	4	12	16	
			44.4%	26.7%	29.6%	
		Total	9	45	54	
			100.0%	100.0%	100.0%	
	> 40 years	Yes	15	81	96	X^2 =13.991 P =0.000
			40.5%	74.3%	65.8%	
		No	22	28	50	
			59.5%	25.7%	34.2%	
		Total	37	109	146	
			100.0%	100.0%	100.0%	
Gender	Male	Yes	13	59	72	X^2 =7.835 P =0.005
			43.3%	72.0%	64.3%	
		No	17	23	40	
			56.7%	28.0%	35.7%	
		Total	30	82	112	
			100.0%	100.0%	100.0%	
	Female	Yes	7	55	62	X^2 =6.699 P =0.010
			43.8%	76.4%	70.5%	
		No	9	17	26	
			56.3%	23.6%	29.5%	
		Total	16	72	88	
			100.0%	100.0%	100.0%	

of culprit artery patency in diabetics was lower in comparison with non diabetics, when treated with thrombolysis i.e streptokinase.

Diabetes mellitus (DM) is associated with a 2- 4 fold increased risk of coronary artery disease, and ischemic coronary artery disease is responsible for three-quarters of diabetes-related deaths[18].In United States alone, almost 65% of diabetic patients succumb to cardiovascular disease[19]. According to GRACE registary[20], in-hospital fatality for ACS was reported almost twice as high in diabetics as in non-diabetics. Likewise, significantly higher all cause mortality was documented for diabetic patients in GUSTO-1 trial both at 30 days as well as 1 yearr post thrombolysis6. Investigators of DIAMOND registry from Korea[21] have also demonstrated that even 2- year MACE rate in patients of acute MI after initial stabilization was significantly higher among diabetics vs non-diabetics (8.0% vs 3.7% with $P < 0.01$). The data shows the major adverse cardiovascular events and mortality is higher in diabetics than non-diabetics. [22]

The poor clinical outcome in diabetes is usually multi-factorial. Diabetics are known to have increased risk of thrombosis due to high platelet reactivity[23]. Silent ischemia or ambiguous symptoms are more common in diabetic patients thereby causing delayed presentation[24]. Additionally, diabetes is associated with more diffuse coronary artery disease, more complex lesion morphologies, poor collateralization and reduced coronary reserve[25].

Most of the previous studies focusing on impact of DM in STEMI patients have assessed the success of reperfusion therapy in terms of ST resolution on ECG following reperfusion. Considering this parameter in a previous study conducted by Sulehria SB et al[26], reperfusion was unsuccessful in 42% of diabetic patients vs 12% non-diabetics while the success of reperfusion therapy was

considerably lower in diabetic patients documented as 58% as compared to 88% in non-diabetics. In another study complete ST-resolution occurred in 31.6% of diabetic and 51.0% of non-diabetic patients, respectively (p< 0.001) [27].

Failure of ST resolution following reperfusion therapy has been consistently reported as less frequent in diabetic vs non diabetics, however, the results have been quite inconsistent when it comes to epicardial flow in culprit artery. As far as angiographic findings are considered, presence of DM has been linked strongly with impairment of myocardial blush grade in some of the prior studies without significant impact on TIMI flow, thereby suggesting MVD as the main reason behind suboptimal outcome of reperfusion therapies in such patients.

In one of these study performed by Angeja et al[28], angiographic and electrocardiographic responses to thrombolytic agents was evaluated in 2588 patients of acute STEMI. Both diabetics as well as non diabetics achieved almost equal rates of epicardial flow, following thrombolysis and adjunctive/rescue PCI (TIMI 3 flow after PCI: 83.7% vs 84.2%, both P = NS).

Zeng Y et al[29] carried out a study on Chinese population to assess the efficacy of Primary PCI with parameters including ST resolution(STR) and myocardial Blush Grade (MBG) in both diabetic and non diabetic subgroups. Their study documented post PCI TIMI III flow in up to 95% patients irrespective of presence or absence of DM. Myocardial blush grade was however significantly different among diabetics vs non diabetics (MBG 0/1, 56.0% vs. 41.1% respectively, P = 0.019) and so was the absence of STR (43.2% vs. 30.7%, P = 0.038) along with a corresponding yet non-significant rise of MACE in diabetics in comparison with non-diabetics (27.4% vs. 16.1%, P = 0.025).

More recent studies have shown high likelihood of lower TIMI flow in culprit arteries of STEMI patients having diabetes. A retrospective assessment of a single-center registry from United Kingdom assessed 2586 patients of STEMI undergoing PPCI over a span of 4 years between March 2005 and September 2009. The findings from this analysis reported that postprocedural TIMI flow grade was lower in culprit artery for diabetic subgroup (p=0.031). Diabetic patients also had higher all-cause mortality at 30 days (p=0.0025) and 1 year (p<0.0001) following PPCI30. Polish Registry of Acute Coronary Syndromes (PL-ACS)31 which was published around same time , reproduced similar findings. A total of 71,290 consecutive patients of ACS were evaluated including both STEMI (37,898) and NSTEMI (33,392). Diabetic patients had lower coronary angioplasty efficacy (TIMI III flow) (67% vs. 75.8%; p = 0.001) compared to those without DM. Both in-hospital mortality (61.4% vs. 55.9%; p = 0.001) as well as 3- year mortality (78.6% vs. 70.7%; p < 0.0001) were significantly higher for diabetics vs non diabetics.

The findings of our study are more consistent with those of above 2 registries[30,31]. Out of 200 patients subjected to thrombolysis, 46 were diabetics and 154 non-diabetics. Diabetic patients therefore comprised 23% of study population. Based on angiographic assessment following thrombolysis, culprit artery patency was documented in 134 (67%) patients. The incidence of culprit artery patency was noted to be lower in diabetics compared to non-diabetics patients (43.5% vs 74.0%) and the difference was statistically significant (p-value = 0.000). Effect modifiers like age and gender have showed statistically significant influence having p-value 0.000 and 0.010 respectively.

Our study has therefore demonstrated that diabetic patients with STEMI, thrombolyed with streptokinase had lower culprit artery patency. This, in turn, can have both short and long term effects on morbidity and mortality. So, we suggest other methods of reperfusion such as Primary PCI should be preferred over thrombolytics in diabetic patients. Meanwhile, a multi-centred study with larger study population should be started in future, to determine the short and long term effects of thrombolytic therapy in terms of morbidity and mortality. Education of diabetic patients regarding ischemic symptoms should be made essential part of treatment to help them understand earlier recognition of symptoms in context of acute MI and also to achieve optimal glycaemic control in general.

CONCLUSION:

Thrombolytic success in terms of culprit artery patency was lower in diabetic vs nondiabetic patients and association was observed in both genders and patients of >40 years age. However, in younger patients (<40 years) such association was not found.

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