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GLYCOPROTIEN 11b/ 111a RECEPTOR INHIBITOR (TIROFIBAN) FOR FAILED THROMBOLYSIS IN ACUTE ST ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT: We studied the feasibility, safety, clinical benefit, efficacy and 30 day outcome in 50 patients receiving tirofiban in patients with failed thrombolysis in acute ST elevation myocardial infarction, and compared with 50 patients for age, gender and infarct location, who did not receive rescue treatment for different reasons. Tirofiban resulted in an overall ST segment elevation, resolution, at 240 minutes in 44 patients (88 %). Incidence of major events during hospitalization was higher in control group. One patient (2 %) died in study group against 4(8%) in control group while 4 patients had refractory angina needing early percutaneous coronary intervention as compared to 13 in control group. None reinfarcted as against 4 in control group. Two patients developed congestive heart failure against 8 in control group. However, minor bleeding events (mainly gum) were significantly higher, 9 against 0 in control group. Coronary angiography revealed residual thrombus only in 4 patients treated with tirofiban compared to 13 in controls and surprisingly the number of stents required were less in study group (74 % *i.e.* 37 patients) against (96 % *i.e.* 48 patients) in control group. On 30 day follow up no death, congestive heart failure or repeat revascularization procedure was recorded in the study group with significant improvement in left ventricular ejection fraction, while as there were 3 deaths and 4 patients had congestive heart failure in control group

INTRODUCTION: Success rate of intravenous thrombolysis is close to 70 %. Therefore stratigies for failed thrombolysis or reocclusion/ reinfarction also need to be planned in advance. Ongoing chest pain, non-resolution of ECG *i.e.* failure of the elevated ST segment to fall by 50% or more in lead with maximal ST elevation recorded 90 minutes after onset of thrombolysis, hemodynamic or electric instability indicate failure of recanalization. Repeat thrombolysis with the same or other agent is not to be practiced.

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A rescue percutaneous coronary angioplasty must be encouraged even though the outcomes of rescue angioplasty are not good. If rescue angioplasty is not available, small molecule Gp IIb/ IIIa inhibitors, tirofiban, eptifibatide can be used as a 24 to 48 hour infusion as a last resort [1 - 4]. With this idea in background, we studied the feasibility, safety, clinical benefits, efficacy and 30 days outcome in patients receiving tirofiban for failed thrombolysis where immediate rescue angioplasty was not possible.

The GP IIb/ IIIa receptor inhibitors are a potent class of antiplatelet drugs that act by preventing the final common pathway of platelet aggregation, *i.e.*, fibrinogen mediated cross linkage of platelets through the GP IIb / IIIa receptor. These agents are potent inhibitors of platelet

aggregation (*e. g*, thrombin, ADP, collagen, serotonin). Tirofiban is a non peptide antagonist of the platelet glycoprotein (GP IIb/IIIa) receptor, which inhibits platelet aggregation. When given according to the recommended regimen, greater than 90 % inhibition is attained by the end of the 30 minutes infusion. Platelet aggregation inhibition is reversible following cessation of the infusion of tirofiban, hydrochloride. Tirofiban also stimulates VEGF expression and promotes proliferation of endothelial cells. VEGF is a well known inhibitor of endothelial cell apoptosis [5].

Glycoprotien IIb/ IIIa inhibitors in the recent past were used as a bridge to rescue transluminal coronary angioplasty in patients with ST elevation myocardial infarction with failed thrombolysis before the arrival of stronger antiplatelets *i.e.* prasugril and ticagrelor. [6, 7]

This study was conducted in the Department of cardiology in a tertiary care hospital of northern India. This was a prospective study and was conducted over a period of two and a half years.

MATERIAL AND METHODS: One hundred Patients of Myocardial Infarction, who fulfilled the criteria for failed thrombolysis, were included in this study. Diagnosis of failed thrombosis was made on symptoms and electrographic criteria *i.e.* persistence or recurrence of chest pain and failure of the elevated ST segment to fall by 50 % or more in lead with maximal ST elevation recorded 90 minutes after onset of thrombolysis [2, 3]. They were randomized into two groups of 50 patients each *i.e.* Study group received tirofiban 120-180 minutes after the end of thrombolysis (0.4ug /kg/ mt for 30 minutes) followed by an infusion of 0.1 ug/kg/mt for 48 hrs. Control group did not receive tirofiban; however they received same adjunctive therapy as the study group.

These two groups of patients were matched for age, gender and infarct location. These two groups of patients were assessed clinically, underwent baseline investigations besides other investigations including ECG - (pre thrombolysis, post thrombolysis, after start of tirofiban *i.e.* 180-240 minutes in study group to look for any resolution of ST segment). Echocardiography was done in both groups during hospitalization and at 30 days follow up. Both groups of patients were subjected to coronary angiography afterwards to look for the status of coronary arteries. Major events during hospitalization were looked for which included: Death, Death from periprocedural complications, refractory ischemia requiring urgent coronary intervention, myocardial reinfarction, congestive heart failure and bleeding events. All the enrolled patients were monitored for 30 days after the index acute event and end points of the study were looked for *i.e*. death, congestive heart failure, repeat revascularization, LVEF % at 30 days, and any other complication.

RESULTS: 50 patients receiving Gp IIb/ IIIa receptor inhibitor (tirofiban) in patients with failed thrombolysis, in acute ST elevation myocardial infarction were compared with 50 patients for age, gender and infarct location, who did not receive rescue treatment for different reasons. Majority of the studied patients were males with age ranging from 40-85 years and mean age of 58.3 ± 11.7. (**Table 1**). Near about 75 % patients were in Killip class 1 and majority were having Anterior wall myocardial infarction (48 %), followed by Anterio - Lateral myocardial infarction (24%), inferior wall myocardial infarction (18 %), Inferior with RV extension (6 %), Inferio-posterior myocardial infarction (4 %), Anterio-septal (4 %) and Inferio-lateral (2 %), (**Table 2** and **3**). The risk factors encountered in study group were smoking (68 %), hypertension (64 %), Dyslipidemia (24 %), Diabetes Mellitus (14 %), & alcoholism (2%), **Table 4**.

There was family history of Hypertension, Diabetes Mellitus and coronary artery disease in 40 %, 2 % and 2 % respectively. The thrombolytic agent used in all patients was Streptokinase **Table 5** and **6**. Tirofiban administration resulted in an overall ST segment elevation, resolution, at 240 minutes in 44 patients (88 %) which is a statistically significant finding. Incidence of major events during hospitalization was higher in control group. One patient (2 %) died against 4 (8 %) in control while 4 patients had refractory angina needing early intervention as compared to 13 in control group. None reinfarcted as against 4 in control group. Two patients developed heart failure against 8 in control group.

However, minor bleeding events (mainly gum) were significantly higher, 9 against 2 in control group **Table 7**. Coronary angiography revealed residual thrombus only in 4 patients treated with Tirofiban compared to 13 in controls and surprisingly the number of diseased vessels was also higher in control group **Table 8**. On 30 day follow up no death, Congestive heart failure or repeat revascularization was recorded in the study group, with significant improvement in left ventricular ejection fraction, while as in control group there were 3 deaths and 4 patients had congestive heart failure.

TABLE 1: DEMOGRAPHIC CHARACTERISTIC OF THE STUDY AND CONTROL GROUPS

		Study		Control		P value
		n	%	n	%	
Gender	Male	45	90.0	43	86.0	
	Female	5	10.0	7	14.0	0.540
Age (years)	Mean ± SD	58.3 ± 11.7 (40,85)		59.3 ± 9.9 (43,76)		0.631

TABLE 2: KILLIP CLASS DIAGNOSIS IN THE TWO GROUPS

Killip Class	Study		Control		P valve
	n	%	n	%	
I	37	74	35	70	0.585 (NS)
II	8	16	7	14	
III	2	4	4	8	
IV	3	6	4	8	

TABLE 3: SITE OF INFARCTION IN THE TWO GROUPS

Diagnosis	Study		Control		P valve
	n	%	n	%	
Anterior Wall MI	24	48	25	50	0.841 (NS)
Anterio-Lateral MI	12	24	12	24	1.000 (NS)
Inferior Wall MI	9	18	7	14	0.585 (NS)
Inferior Wall MI with RV Extention	3	6	1	2	0.307 (NS)
Inferio- Posterior MI	2	4	2	4	1.000 (NS)
Anterio-Septal MI	2	4	2	4	1.000 (NS)
Inferio- Lateral MI	1	2	2	4	0.558 (NS)

TABLE 4: RISK FACTOR PROFILE IN THE TWO GROUPS

Factor	Study		Control		P valve
	n	%	n	%	
Smoking	34	68	28	56	0.219
Hypertention	32	64	29	58	0.541
Diabetes Mellitus	7	14	9	18	0.587
Dyslipidemia	12	24	10	20	0.631
Alcoholic	1	2	0	0	0.317

TABLE 5: FAMILY HISTORY IN THE TWO GROUPS

F/H	Study		Control		P valve
	n	%	n	%	
Hypertension	20	40	23	46	0.547
Diabetes Millitus	1	2	2	4	0.560
Coronary artery disease	1	2	0	0	0.317

TABLE 6: THROMBOLYTIC AGENT USED IN THE TWO GROUPS

Thrombolytic Agent used in the Studied Subjects				
Thrombolytic Agent	Study		Control	
	n	%	n	%
Streptokinase	50	50.0	50	50.0

TABLE 7: MAJOR EVENTS DURING HOSPITALIZATION IN THE TWO GROUPS

Response	Study		Control		P valve
	n	%	n	%	
Death	1	2	4	8	0.171
Refractory Ischemia	4	8	13	26	0.017
Death from Periprocedural complication	0	0	1	2	0.317
Myocardial reinfarction	0	0	4	8	0.041
Congestive Heart failure	2	4	8	16	0.046
Bleeding Event	9	18	2	4	0.026

TABLE 8: CORONARY ANGIOGRAPHIC FINDINGS IN THE TWO GROUPS

Disease	Study		Control		P valve
	n	%	n	%	
SVD	19	38.0	22	44.0	0.022 (sig)
DVD	18	36.0	24	48.0	
TVD	2	4.0	3	6.0	

DISCUSSION: Reperfusion strategies in the early phase of treatment of acute ST elevation myocardial infarction aim to rapidly normalize and maintain tissue perfusion. Primary angioplasty is probably the best current treatment but it can only be applied to a minority of patients and has its own problems. Thrombolysis remains the most commonly used treatment. It has well demonstrated benefits, saving lives and reducing left ventricular damage, but is far from perfect. In a considerable number of patients, however, this therapy fails to relieve symptoms, fails to achieve TIMI 3 flow or fails to restore ST - segment elevation, while in other patients reinfarction occurs early, within 24 hrs or in subsequent days.

Various rescue therapies have been considered in so - called failed thrombolysis, and in particular, rescue percutaneous coronary intervention [8, 9] and rescue lysis.[10, 11] Given the importance of the platelet component of the thrombus in explaining thrombus resistance to lyses, rescue therapy with glycoprotein Gp IIb/ IIIa receptor blockers in patients in whom thrombolysis has failed may be an attractive strategy.[12 - 14]

In our study 100 patients of acute Myocardial infarction who met the criteria of failed thrombolysis were randomized (single blind) into 2 groups of fifty patients each *i.e.* study and control group. An electrocardiogram was obtained at 180 - 240 minutes in all patients after the beginning of tirofiban infusion, which revealed ST - segment resolution in 44 (88%) in study group where as only 2 patients (4 %) in the control group had resolution of ST segment of more than 50 %.

All the patients who received tirofiban had a resolution of chest pain where as all the patients in the control group had either persistence or recurrence of chest pain. During hospitalization there was 1 death, no patient had myocardial reinfarction, 4 patients (8 %) had refractory ischemia who needed percutaneous coronary revascularization. Of the 2 patients (4 %) who presented with congestive heart failure at the beginning of treatment, 1 recovered within few hours, while 1 patent died. 9 patients (18 %) had bleeding, which was minor.

Out of these 9 patients, 5 had gingival bleeding, 2 had minor hemoptysis and 2 had hematuria. All patients who were discharged from hospital were alive at the 30 - days follow up and no patient had congestive heart failure and all discharged patients in the study group had improvement in ejection fraction. All these events except for bleeding were significantly higher in the control group. Incidence of death during hospitalization was also high in the control group. In a study conducted by Vetrano, Corotenuto *et al*., [13].

The clinical outcome of 48 consecutive patients with myocardial infarction who received tirofiban for unsuccessful thrombolysis was compared with that of 48 patients matched for age, gender, and infarct location who did not receive rescue treatment. Those who received tirofiban had more successful reperfusions, few bleeding complications and no death was recorded in these patients at 30 day follow up. They also found an overall ST-segment elevation resolution at 240 minutes in 75 % of patients.

In the GUSTO 111 trial, a subset analysis of 387 patients who underwent rescue percutaneous transluminal coronary angioplasty after failed thrombolysis had a mortality rate at 30 days of 3.7 % in 81 patients who received periprocedural Gp IIb/ IIIa receptor inhibitor, compared with a rate of 9.8 % in the 306 patients who did not receive periprocedural Gp IIb/ IIIa receptor inhibitor at a cost of an increased incidence of severe bleeding [14]. The early normalization of ST segments and the disappearance of the chest pain as seen in our study, reflects the adequate myocardial reperfusion obtained from dissolution of the platelet components.

Furthermore; the reduction in clinical events reflects that, as in experimental data, glycoprotein Gp IIb/ IIIa receptor inhibitor leads to a more stable residual thrombus and avoids cyclic flow variations and repeat thrombosis [15, 16]. Pasquale, Sarullo *et al.*,[17] studied the effectiveness of glycoprotein Gp IIb/ IIIa receptor inhibitors in acute myocardial infarction patients in case of unsuccessful and failed thrombolysis. They found that these patients showed rapid reperfusion, patency of infarct related artery on coronary angiography with reduced incidence of stent treatment. A higher bleeding rate in patients receiving glycoprotein Gp IIb/ IIIa inhibitor as an adjunct to rescue therapies for failed thrombolysis is well documented [6, 14]. **1**

Data suggest a substantial clinical benefit of glycoprotein Gp IIb/ IIIa inhibitor use over thrombolysis with an acceptable bleeding risk in patients not undergoing immediate rescue revascularization [17 - 19]. Petronio *et al.*, [18]. Studied the efficacy of Gp11b/ 111a inhibitor (abciximab) during rescue percutaneous coronary intervention in 79 patients. They found that these patients showed a significantly better improvement at 1 month of follow up in the echocardiographic left ventricular wall motion score.

In our study a significant improvement in left ventricular ejection fraction was found at 30 day follow up. As of now benefit of Gp IIb/ IIIa inhibitors appears to be limited to lesions with large thrombus burden. In a head to head comparison of tirofiban with urokinase in emergency percutaneous coronary intervention with large thrombus burden, coronary thrombi in tirofiban group disappeared earlier than that of urokinase group; the incidence of bleeding was comparable between two groups [20]. In patients with large anterior ST elevation MI presenting early after symptom onset and undergoing primary PCI, infarct size at 30 days was significantly reduced by bolus intracoronary abciximab delivered to the infarct lesion site but not by manual aspiration thrombectomy [21]. Advent of rapidly acting thienopyridine-prasugrel and ticagrelor, has further restricted the use of Gp IIb/ IIIa inhibitors.

However, there is still scope of these agents especially tirofiban infusion in a patient population as of ours where immediate rescue angioplasty is not possible either because of technical reasons or because of financial constraints.

CONCLUSION: In patients of acute MI with failed thrombolysis, treatment with tirofiban is feasible & of clinical benefit. Increase in the risk of bleeding can be considered acceptable as it was of minor nature and also in view of adequate reperfusion achieved.

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