

Very Early versus Early Invasive Strategy after Successful Thrombolysis in Patients with ST Segment Elevation Myocardial Infarction

Abstract

Background: Till this time even with superiority of primary percutaneous coronary intervention (pPCI) in the management of ST segment elevation myocardial infarction (STEMI), most of patients present to hospitals without pPCI facilities receive fibrinolytic therapy. The current recommendations support routine early invasive strategy within 24 hours.

Objectives: we aimed at evaluating the best timing of invasive strategy within the first 24 hours.

Methods: The study was conducted on 60 STEMI patients who were referred to our center after successful thrombolysis. Patients were randomized into 2 groups: Very early invasive group (n=30): subjected to very early invasive strategy within 3 to 12 hours post thrombolysis. Early invasive group (n=30): subjected to early invasive strategy within 12 to 24 hours. The primary endpoints were the composite endpoints of major adverse cardiac events (MACEs). Secondary endpoints were achievement of TIMI III flow with MBG II or III. Safety endpoints were bleeding complications.

Results: Both groups were homogenous regarding the demographic, clinical, and angiographic data before invasive strategy. TIMI III flow and MBG II or III were achieved in 83.3% of patients in the very early invasive group vs. 86.6% in the early group (P = 0.955). There was no difference between both groups regarding the composite endpoints MACEs (P= 0.667) or bleeding complications (P=0.528).

Conclusion: The study did not demonstrate a correlation between magnitude of benefit and timing of early PCI post successful thrombolysis in patients with STEMI. Thus, early invasive strategy could be scheduled depending on the logistics of the reference catheterization laboratory within 24 hours post thrombolysis.

Keywords: Acute MI; Fibrinolytic therapy; Thrombolysis; Early invasive

Research Article

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Introduction

Primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) has been shown to be preferable to thrombolytic therapy in terms of patient survival, higher rates of patency in the infarcted arteries, and lower rates of reinfarction and stroke [1,2].

Till this time even with superiority of primary PCI most of patients with ST-elevation myocardial infarction (STEMI) present to hospitals without PCI facilities and receive fibrinolytic therapy. Early post thrombolysis referral had been discouraged in the past; however multiple studies were performed comparing immediate or early angiography after fibrinolysis versus a more conservative strategy of deferred PCI or ischemia-guided management showed evidence for a reduction in the risk of total mortality in patients undergoing immediate or early PCI with no significant differences in the risk of stroke or major bleeding [3,4].

Thus, early referral for angiography with subsequent PCI (if indicated) should be the standard of care after thrombolysis:

the so-called 'pharmacoinvasive' strategy. A crucial issue is the optimal delay between lysis and PCI. There was a wide variation in delay in trials, however a time window of 3–24 h after successful lysis is preferred [5-7]. This strategy is now considered Class IIa level of evidence A in the recent ESC guidelines for STEMI [8] and level of evidence B in the recent ACC/AHA guidelines for STEMI [9].

These data support the current recommendation for routine early invasive strategy in STEMI patients after successful fibrinolysis but the best timing for referral to invasive strategy still needs to be studied more in randomized trials.

Methods

Patients

200 patients with ST-segment elevation myocardial infarction (STEMI) were referred to our tertiary PCI center after receiving thrombolytic therapy outside our center between October 2013 and October 2014.

This randomized controlled study was conducted on 60 patients out of 80 patients who had successful reperfusion after thrombolytic therapy to either very early invasive strategy (3-12 hours) or early invasive strategy (12-24 hours) (Figure 1).

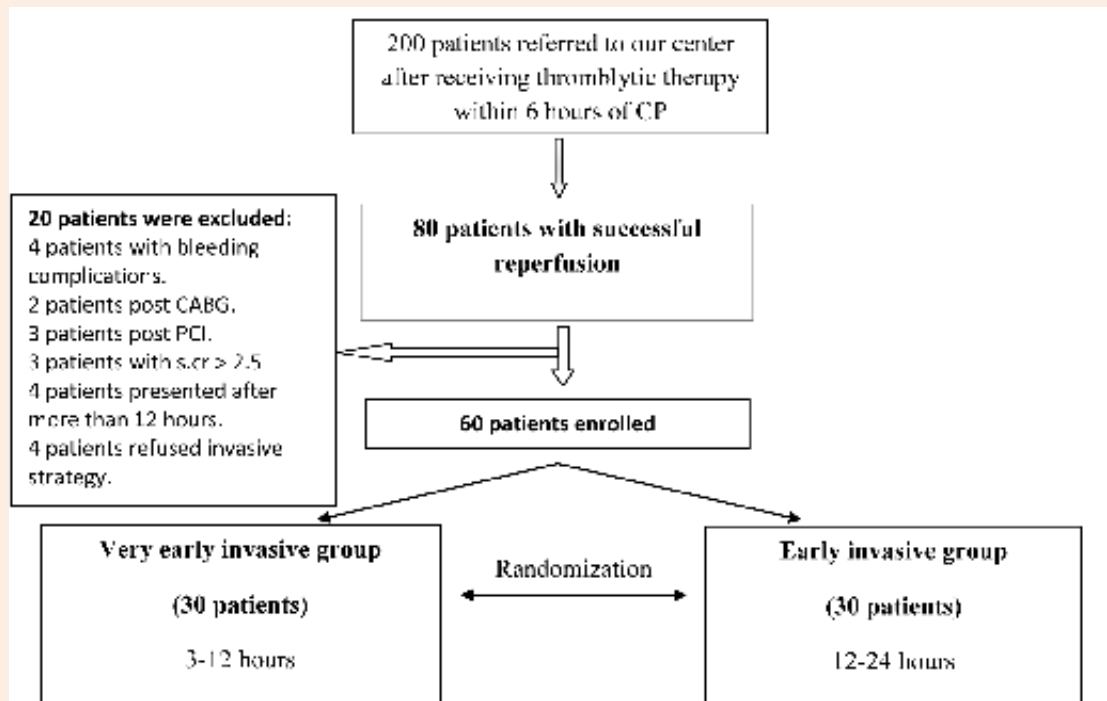


Figure 1: Study flowchart.

The study population consisted of patients aged 18-70 years who presented to another hospital without PCI facility within 6 hours of acute chest pain and STEMI, those patients received fibrinolytic therapy (streptokinase 1.500 million IU in most of the cases) as an early management then referred to our tertiary center, patients who had subsequent criteria indicative of successful reperfusion were enrolled in the study. The early criteria for successful reperfusion included: Resolving of more than 50% of ST segment elevation at 60-90 minutes, [10], Relief of chest pain within 60-90 minutes from initiation of thrombolysis [11]. Patients with one or more of the following criteria were excluded from the study: Failed reperfusion post thrombolysis, any indication requiring rescue PCI (cardiogenic shock, acute pulmonary edema, persistent chest pain, malignant arrhythmias), Mechanical complications (acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), cardiac rupture), moderate and severe renal impairment (estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m² using MDRD equation), post coronary artery bypass grafting (CABG) and post PCI patients, patients with previous STEMI or LV dysfunction, post thrombolysis major bleeding complications (intracranial bleeding, gastrointestinal bleeding), patients who received thrombolytic therapy after more than 6 hours of chest pain or presented more than 12 hours after successful thrombolysis (Lack of randomization),

contraindications for antiplatelets such as bleeding disorder or known any bleeding tendency either inherited or acquired and thrombocytopenia (Platelet count < 100.000/cm³).

The included patients were randomized into two groups according to the timing of the early invasive PCI (the randomization table was generated using www.randomsequencegenerator.org):

Group I (very early invasive group): 30 patients were referred to invasive strategy after 3 hours and within 12 hours after successful thrombolysis.

Group II (early invasive group): 30 patients were referred to invasive strategy after 12 hours and within 24 hours after successful thrombolysis.

The study was approved by the local ethics committee; as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013 and all patients signed a written informed consent before the procedure.

Study protocol

All patients were subjected to the following: history analysis emphasizing on age, sex and presence of risk factors (smoking, hypertension, diabetes, dyslipidemia and positive family history

of premature CAD), proper analysis of chest pain regarding time of maximum intensity, time from symptom onset to presentation to the other hospital (pain to door), time from presentation to thrombolysis (door to needle) and finally timing from thrombolysis till arrival to our hospital (transfer time), history of any other co morbidities and presence of any of the exclusion criteria. Complete physical evaluation was done for all the patients on admission and during their hospital stay with recording of any abnormality especially hemodynamic data, Killip class (Class 1: patients with no abnormal clinical findings, Class 2: patients with pulmonary congestion, elevated jugular venous pressure or having S3 gallop, Class 3: patients with pulmonary edema, Class 4: patients with cardiogenic shock), mechanical complication (MR, VSR) and any neurological deficit. Routine labs were done for all patients according to clinical scenario with serial cardiac enzymes, serum creatinine and complete blood count during hospital stay.

ECG: Twelve leads surface ECG was done for all patients on admission and at 90 minutes post thrombolysis and was compared to the first ECG in the other hospital and was related to the time of thrombolysis aiming to recruit patients with successful fibrinolytic therapy after 90 minutes by the pre-specified criteria to any of the study groups or referring patient with failed thrombolysis to immediate rescue PCI, then serial ECGs were done during follow up periods according to clinical scenario.

Patient preparation: All Patients received 300 mg aspirin, 600 mg clopidogrel and fibrinolytic therapy (streptokinase 1.500 million IU in most of the cases). Patients with successful reperfusion were randomly divided into 2 groups: very early invasive group (3-12 hours) or early invasive group (12-24 hours).

Angiographic data: Coronary angiography and subsequent needed intervention for the culprit vessel was done for each patient according to the index time of each study group with the following data obtained: Culprit and other vessel affection, site of the lesion, type of the lesion according to AHA/ACC classification system into 3 types A, B and C, [12] the degree of stenosis, thrombus burden, [13] TIMI flow, [14] and myocardial blush grade (MBG) [15] were assessed.

N.B. lesion length was measured shoulder-to-shoulder in an unforeshortened view.

Intra and Post procedural data and medications: Intracoronary medications were given at the discretion of the operator. Glycoprotein (GP) IIb IIIa inhibitors were given in very limited cases due to previous streptokinase treatment only as a bailout therapy in patients in which TIMI flow post procedural less than or equal to TIMI II flow. The treatment was continued for 12-24 hours. IV unfractionated heparin (UFH) was given during the PCI procedure (70-100 IU/Kg) maintaining activated clotting time > 250 seconds (hemotech device). Pre and post dilatation, stent type, length and diameter, post stenting TIMI flow and MBG were recorded, no/slow reflow during the procedure was defined as a final TIMI flow < 2 or TIMI flow 3 with a MBG < 2 in the culprit artery, in the absence of anatomic vessel stenosis or obstruction, flow-limiting dissection, spasm, or thrombus [16].

All patients continued on 150 mg aspirin, 75 mg clopidogrel daily for one year post procedure. Other medications, including

β -blockers, ACE inhibitors, nitrates, statins, heparin and morphine were administered at the discretion of the attending physicians according to the current guidelines. Routine echocardiography was done for all patients (from the third to the fifth day post PCI) with special emphasis on ejection fraction (EF) calculated by Biplane Simpson Method (LV internal volumes), and any mechanical complications. Duration of hospitalization was reported with 1 month follow up after hospital discharge for primary and secondary end points.

End points

The Primary end points were composite end point of major adverse cardiac events (MACE) death, re infarction, recurrent ischemia, and target vessel revascularization. Secondary end points included achievement of TIMI III flow with MBG II or III. Safety end points were the occurrence of major bleeding or hemorrhagic complications or occurrence of hemorrhagic stroke. Bleeding was classified according to Gusto classification: Grade I: severe bleeding: documented intracranial hemorrhage or bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support or surgical intervention. Grade II: moderate bleeding: bleeding that requires transfusion of blood but does not lead to hemodynamic compromise requiring intervention. Grade III: mild bleeding: bleeding not requiring transfusion and not causing hemodynamic compromise. This includes subcutaneous bleeding, mild haematomas, oozing from puncture sites, etc.¹⁷

Statistical analysis

Data were collected, verified, revised and then edited on the P.C. The data were then analyzed statistically by using SPSS statistical package version (16). Continuous variables are expressed as the mean \pm standard deviation (SD), while discrete variables are presented as absolute values, percentages, or both. Continuous variables were compared with Student's t-test. Discrete variables were compared with the chi-square test. The comparison between two groups with quantitative data and parametric distribution were done by using independent t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following, P > 0.05: non-significant, P < 0.05: significant and P < 0.001: highly significant.

Results

Out of 200 STEMI patients who referred to our tertiary center after receiving thrombolytic therapy in other hospitals, 60 patients with successful thrombolysis were enrolled. 30 patients were randomly assigned for very early invasive PCI strategy after 3 hours till 12 hours post thrombolysis (very early invasive group), and 30 patients for early invasive strategy after 12 hours till 24 hours (early invasive group).

The basic characteristics including demographic data, risk factors, chest pain duration (pain to door time), door to needle time and transfer time were well balanced in both study groups (Table 1). Most of the patients in both study groups were in Killip class I and most of them had anterior STEMI (76.7% vs 56.7% P= 0.170). Patients in both groups showed around 60% ST segment resolution after thrombolytic therapy and around 70% of them

showed very early peaking of cardiac enzymes after 8 hours indicating successful fibrinolytic therapy (Table 1). The mean time to intervention in the very early invasive group was 5.3±6.5 hours versus 18.35.4 in the early invasive group P<0.001 (Table 2). The angiographic and procedural details including access site, culprit vessel, type of lesion, number of vessels affected, TIMI thrombus

grade, initial TIMI flow, use of GP IIb/IIIa inhibitors, thrombus aspiration, PTCA before stenting, stent type, diameter and length, inflation pressure and need for post deployment were matched in very early and early invasive groups (Table 2). Most of patients in both groups had TIMI II flow post successful thrombolysis.

Table 1: Basic characteristics of the study population.

Variable	Very Early invasive (n=30)	Early Invasive (n=230)	P-value
Age (years), mean±SD	58.5±8.8	59.8±8.3	0.558
Male gender, no (%)	20 (66.7%)	24 (80%)	0.381
Smoking, no (%)	16 (53.3%)	20 (66.7%)	0.429
Hypertension, no (%)	11 (36.7%)	9 (30%)	0.784
Diabetes, no (%)	14 (46.7%)	13 (43.3%)	0.795
Family history, no (%)	6 (20%)	3 (10%)	0.469
Dyslipidemia, no (%)	12 (40%)	14 (46%)	0.794
eGFR by MDRD (mL/min/1.73m2), mean±SD	96.3±7.8	97.6± 8.4	0.536
Peripheral vascular disease, no (%)	0 (0.0%)	0 (0.0%)	NA
Killip class, no (%)			0.471
Killip 1	24 (80%)	27 (90%)	
Killip 2	6 (20%)	3 (10%)	
Killip 3 and 4 (excluded)	0 (0%)	0 (0%)	
Pain-to-door (hours) mean±SD	4.7±1.54	3.9±2.1	0.097
Door-to-needle (minutes) mean±SD	34.5±13.9	34±13.5	0.888
Transfer time (hours) mean±SD	7.3±3.5	6.9±4.1	0.685
Number of leads with ST segment elevation (mean±SD)	5.4±1.16	5.6±1.1	0.495
Magnitude of sum of ST segment elevation (mm) mean±SD	17.5±4.7	19.6±5.7	0.124
Anterior STEMI, no (%)	23(76.7%)	17(56.7%)	0.17
Streptokinase used, no (%)	29 (96.67%)	28 (93.3%)	0.553
Resolution in max. ST segment elevation (%) mean±SD	62.43±16.5	63.2±17.85	0.862
Resolution in sum ST segment elevation (%) mean±SD	52.15±16.4	54.45±17	0.595
Peak CK (U/L) mean±SD	2247.63±875.27	2223.18±848.51	0.912
Peak CK-MB(U/L) mean±SD	286.86±126.89	271.9±104.8	0.62
Patients with early peaking < 8 hours, no (%)	21 (70%)	19 (63.3%)	0.784

Table 2: Baseline Angiographic and interventional data.

Variable	Very Early Invasive(n=30)	Early Invasive (n=30)	P-value	
Radial access no (%)	5 (83.4%)	3 (10%)	0.704	
Mean time to intervention post thrombolysis (hours) mean±SD	5.3±6.5	18.3±5.4	<0.001	
Culprit vessel: no (%)	17 (56.7%)	4 (13.3%)	9 (30%)	
LAD	23 (76.7%)		0.17	
LCX	2 (6.7%)		0.667	
RCA	5 (16.7%)		0.359	
Type of culprit lesion, no (%)				
Type A	0 (0%)	3 (10%)	0.236	
Type B	19 (63.3%)	16 (53.3%)	0.6	
Type C	11 (36.7%)	11 (36.7%)	1	
Number of vessel affected:				
no (%)				
One vessel	19 (63.4%)		0.784	
Two vessels	6 (20%)		0.754	
Three vessels	5 (16.6%)		0.421	
TIMI thrombus Grade: no (%)	Grade 0	2 (6.7%)	5 (16.7%)	0.421
	Grade 1	12 (40%)	15 (50%)	0.603
	Grade 2	9 (30%)	7 (23.3%)	0.77
	Grade 3	4 (13.3%)	2 (6.7%)	0.667
	Grade 4	3 (10%)	1 (3.3%)	0.604
	Grade 5	0 (0%)	0 (0%)	NA
TIMI flow before angioplasty, no (%)				
TIMI 0	0 (0%)	0 (0%)	NA	
TIMI I	5 (16.7)	2 (6.7%)	0.421	
TIMI II	24 (80%)	25 (83.3%)	0.738	
TIMI III	1 (3.3%)	3 (10%)	0.604	
Procedural details, no (%)				
GP IIb/IIIa inhibitors	3 (10%)	2 (6.7%)	0.64	
PTCA	5 (16.6%)	7 (23.3%)	0.746	
Thrombus aspiration	2 (6.7%)	1 (3.3%)	0.553	
Stent details:				
Type Drug eluting, no (%)	23 (76.7)	24 (80%)	0.754	
Stent length (mean±SD)	19.96±4.75	19.7±6.23	0.856	
Stent diameter (mean±SD)	3.23±0.31	3.14±0.369	0.31	
2 stents used, no (%)	6 (16.6%)	4 (13.3%)	0.73	
Inflation pressure (mean±SD)	13.6±1.58	12.8±2.74	0.172	
Post deployment, no (%)	14 (46.7%)	17 (56.7%)	0.605	

Post procedure angiographic analysis and outcome:

TIMI III flow and MBG (II/III) were achieved in 83.3% of patients in the very early invasive group and 86.67% of patients in early invasive group (P = 0.955) with few patients had slow/no reflow (Table 3) (Figure 2). The primary composite end points of MACE were similar (6.67% in very early invasive groups VS.

13.3% in early invasive group P=0.667) (Table 3) (Figure 3). The LVEF was 40.464.7 in the very early invasive group vs. 42.64.9 in the early invasive group (P= 0.089), with no difference regarding duration of hospitalization (Table 3). Regarding safety endpoints, patients in the very early invasive group suffered from minor bleeding 10% vs. 6.76% in the early invasive group and major bleeding 0% vs. 3.3% (P=0.528).

Table 3: Post procedural angiographic analysis and outcomes.

Variable	Very Early Invasive(n=30)	Early Invasive (n=30)	P-value
TIMI flow post PCI, no (%)			0.796
TIMI 0	1 (3.3%)	1 (3.3%)	
TIMI 1	1(3.3%)	0 (0%)	
TIMI 2	2 (6.6%)	2 (6.7%)	
TIMI 3	26 (83.3%)	27 (90%)	
MBG post PCI, no (%)			0.955
MBG 0	4 (13.3%)	3 (10%)	
MBG 1	1 (3.3%)	1 (3.3%)	
MBG 2	11 (36.67%)	10 (33.3%)	
MBG 3	14 (46.67%)	16 (53.4%)	
Slow/no reflow, no (%)	5 (16.67%)	4 (13.3%)	0.717
Duration of hospitalization (days) mean±SD	3.96±0.55	3.93±0.73	0.858
Echocardiographic data:			
EF (Biplane Simpson) mean±SD	40.46±4.7	42.6±4.9	0.089
LVESD (mean±SD)	49.87±2.75	48.96±2.55	0.189
LVEDD (mean±SD)	56.06±3.17	55.6±3.05	0.569
Significant MR, no (%)	3 (10%)	4 (13.3%)	0.687
VSR, no (%)	0 (0%)	0 (0%)	NA
Apical LV thrombus, no (%)	0 (0%)	1 (3.3%)	0.313
Primary end points:			
Composite end points, no (%)	2 (6.67%)	4 (13.3%)	0.667
Death, no (%)	1 (3.3%)	0 (0%)	0.313
Re-infarction, no (%)	0 (0%)	1 (3.3%)	0.313
Recurrent ischemia, no (%)	1 (3.3%)	2 (6.67%)	0.553
TVR, no (%)	0 (0%)	1 (3.3%)	0.313
Secondary end points: no (%)			0.528
Grades of bleeding:			
Grade I (severe)	0 (0%)	1 (3.3%)	
Grade II (moderate)	1 (3.3%)	0 (0%)	
Grade III (mild)	3 (10%)	2 (6.67%)	

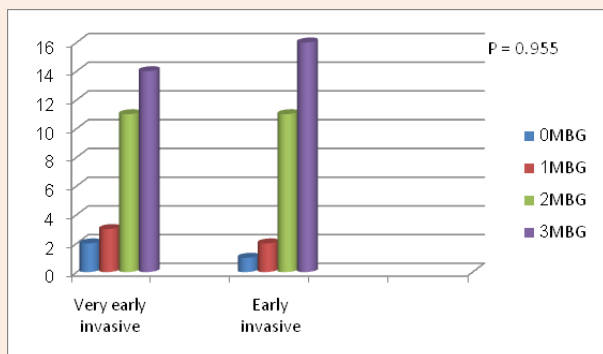


Figure 2: Diagrammatic representation of MBG after in both groups.

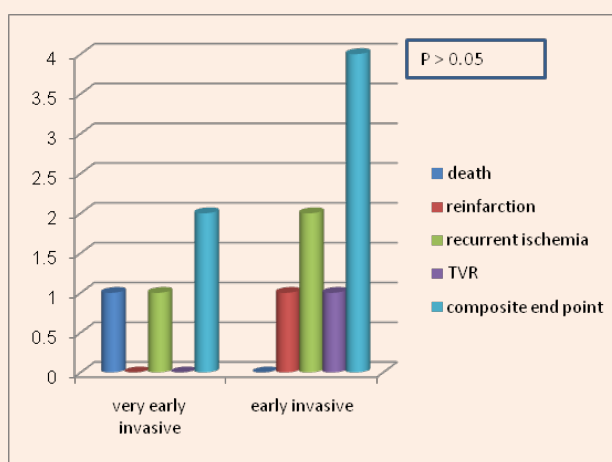


Figure 3: MACEs among both groups.

Discussion

This study is a single center, randomized study that was performed to assess the efficacy and safety of very early versus early coronary angioplasty for infarct related artery after successful thrombolysis in patients presenting with STEMI to determine the best timing for invasive strategy post successful thrombolysis. By reviewing all the previous studies there was no study that compared two timing strategies within the first 24 hours post thrombolysis.

That is why there was marked heterogeneity among different trials in defining the early and late PCI groups. For example; Cantor WJ et al., in the TRANSFER AMI defined early PCI as immediate transfer of the patients post thrombolysis and to intervene in a period less than 6 hours, [5] while Di Mario C et al. [6], in the CARESS-IN AMI trial defined early PCI as performance of intervention within 3.5 hours from hospital admission [6]. The definition of early PCI group in the GRACIA-1 trial was extended up to 24 hours from thrombolysis [18].

In our study we divided the optimum window of routine early intervention post thrombolysis into two groups, a very early group who performed the post thrombolysis intervention 3-12

hours and an early group who performed the intervention 12-24 hours. Since no other studies were designed to lay bare the assumption that very early revascularization might be superior compared to the early one, within the first 24 hours. Accordingly, our study could be considered a pilot study, introducing an idea that could improve the outcome in patients having acute myocardial infarction.

In this work there was no significant difference between very early and early revascularization regarding the primary composite endpoints of MACE and secondary endpoints of procedural success (TIMI III flow and MBG II or III), as well as safety endpoints. All the baseline demographic and clinical data were homogenous between both groups and these results matched with those in the TRANSFER -AMI study where all the Baseline characteristics were well balanced between the two groups except that there was a higher prevalence of previous stroke or transient ischemic attacks in the early-PCI group than in the standard treatment group and a higher prevalence of previous congestive heart failure in the standard-treatment group than in the early-PCI group, and this may be due to higher age group, previous STEMI, previous LV dysfunction and higher Killip class III and IV [5]. The non significant difference between the comparable groups regarding the demographic and clinical data was the same finding in eight randomized controlled trials that were included in a large Meta-analysis done by D'Souza et al. [3].

The analysis of the duration from symptom onset to presentation of patients and from presentation to lytic therapy was done retrograde in most of patients who were referred to us after successful thrombolysis from other hospitals. Despite of the fact that not all patients presented to the same institute; the statistical analysis of these time intervals showed no significant difference between both groups as all referred patients were transferred from high volume centers that are highly qualified in dealing with patients with STEMI. This homogeneity between both groups empowers the study due to the paramount importance of time on the potential benefits of revascularization.

The mean and standard deviation of the time from symptom onset to presentation is considered to be comparable to other studies in which this time duration varied from at least 20 min in the WEST study and up to 12 h in the TRANSFER-AMI, [5] CARESS-AMI, [6] GRACIA-I, [18] and SIAM III [19] studies. Both groups achieved adequate results regarding the TIMI flow and MBG with no timing superiority in the first 24 hours. This outcome was consistent with that occurred in the early PCI group in the TRANSFER AMI study which encourage early intervention in first 24 hours [3]. The assessment of LV systolic function showed no difference between both groups. The relatively low EF despite successful thrombolysis and early revascularization may be explained by the early performance of the echocardiography with the possibility of stunning of the myocardium, besides the culprit vessel in both groups was mainly the LAD (76.7% in the very early group vs. 56.7 in the early group p= 0.170) and so more segments of myocardium were jeopardized.

The duration of follow up (1 month) was the same in the WEST trial however in all other trials enrolled in a large metanalysis by Borgia et al., both clinical (death, re infarction, the combined endpoint of death/ reinfarction, recurrent ischaemia, revascularization) and safety endpoints (major bleeding and

stroke) were assessed at 30 days, whereas only clinical endpoints were assessed at 6–12 months [4]. The trials that addressed the timing issue post thrombolysis (The WEST, [20] NORDISTEMI, [7] TRANSFER AMI, [5] CAPITAL AMI, [21] CARESS-IN-AMI [6] and GRACIA1 [18]) showed significant difference between comparable groups regarding the composite end point of death/reinfarction/recurrent ischemia favoring routine early PCI group over ischemia driven delayed PCI. The advantage of routine early angioplasty over the delayed ischemia driven PCI group was shown despite the variation of time from lytic therapy to PCI which varied from 3 hours in most of these studies to 13 hours in the GRACIA 1 trial [18]. That is why when comparing the results of these studies to our work it should be put into consideration that the two groups in our study were within the optimum window of intervention post thrombolysis and this may be the explanation why there was no significant difference between the two groups regarding the composite end point.

The results of our study was supported by a regression analysis of a large meta analysis by D'Souza et al. [3] to identify the optimal timing for early PCI after fibrinolysis and the subgroups more likely to benefit. This analysis did not demonstrate a correlation between magnitude of benefit and timing of early PCI. Thus, this study concluded that PCI could be scheduled depending on the logistics of the reference catheterization laboratory. The mortality that occurred in patient number 5 in group 1 during intervention was not related to the efficiency of reperfusion by streptokinase as signs of successful thrombolysis were documented by history, ECG and cardiac enzymes, the mortality in this patient could be explained by his young age, heavy smoking, the culprit vessel was the LAD, the non culprit vessels were of normal caliber and slow flow with no ischemic preconditioning to establish collaterals to support the myocardium raising the possibility of large thrombus on top of non significant plaque. His initial TIMI flow was TIMI I and the post procedural TIMI flow was TIMI 0.

The incidence of death is an uncommon event in all trials that compared routine early angiography to other groups. Its incidence does not exceed 3.8% in either groups as shown in the two large meta analysis done by Borgia et al. [4] and D' Souza et al. [3] Most cases of death occurred before day 5 in the early PCI group while in the standard conservative group most cases occur after day 3 as mentioned in the study by Di Mario C et al. [6], Cantor WJ et al. [5] stated that all cases of mortality occurred in patients presenting in killip class 4.

The possible explanation for reinfarction that occurred in patient (number 3 in group 2) after 16 days from discharge was stopping of all medications including clopidogrel because of financial issues. Recurrent ischemia was identified in 3 patients: patient number 6 in group I and patient number 10 and 11 in group 2. The possible explanation for patient number 6 in group 1 who developed chest pain in the first and second day of admission was the slow flow and or the presence of critical lesion in non culprit diffusely diseased small caliber OM branch. The same was for patient number 10 in group II due to the presence of critical filling defect lesion in non culprit medium sized diffusely diseased diagonal branch and the decision in both patients was to maximize medical treatment, while the third patient (number 11 in group II) the cause of recurrent ischemia after 4 weeks was the presence of significant in-stent restenosis in proximal LAD as shown by coronary angiography done after positive stress ECG. This patient

had higher risk of restenosis due to long standing diabetes, small diameter of the vessel (2.75) and long lesion (33mm).

Regarding recurrent ischemia and TVR, Worth mentioning that most of the trials in the stent era that compared routine early invasive strategy with other strategies used bare metal stents [3,4] except only one study the GRACIA 3 used paclitaxel eluting stents [22]. This might raise the suspicion that the results of these studies might have been different if DES were used. There were no patients complicated by cardiogenic shock and or heart failure or ischemic stroke, possibly this was related to the study design where patients >70 years, previous STEMI, LV dysfunction, Killip class III and IV were excluded.

Regarding the safety end points, there was no difference between both groups regarding bleeding complications. One patient (number 2 in group two) was complicated by subarachnoid hemorrhage. This complication may be attributed to the baseline characteristics of this patient, as he was considered to be at a higher risk of bleeding than other patients due to his age (69 years), low body weight (65 Kg) and creatinine clearance (49).

Trials in the pre stent era showed increased incidence of major bleeding and hemorrhagic stroke in the early PCI group as in the TAMI I trial [11] and TIMI IIA trial [23], however recent trials as The (WEST, NORDISTEMI, TRANSFER AMI, CAPITAL AMI, CARESS-IN-AMI and GRACIA1 trials) showed no increased risk of minor or major bleeding [4]. This may be related to the use of smaller sheaths, earlier removal of sheaths, radial access, the administration of lower doses of anticoagulants, and the elimination of post procedural heparin infusions [24]. Also the use of highly fibrin-specific fibrinolytic agents such as tenecteplase is associated with lower rates of non cerebral bleeding [25,26].

Study Limitations

Though, no significant differences were noticed between both groups regarding the primary, secondary and safety end points but this study is a single center pilot study included limited number of patients (n=60) with short period of follow up (1 month) which prevent it to detect intermediate and long term clinical and echocardiographic benefits of any of the timing protocol. Also we did not use other modalities to assess myocardial salvage as SPECT or MRI which may help to detect any superiority in one group.

Conclusion

The study did not demonstrate a correlation between magnitude of benefit and timing of early PCI post successful thrombolysis in patients with STEMI. Thus, early invasive strategy could be scheduled depending on the logistics of the reference catheterization laboratory within 24 hours post thrombolysis.

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