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Comparison between Pharmaco-invasive Strategy and Primary Percutaneous Coronary Intervention According to Percutaneous Coronary Intervention Related Delay

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Authors' contributions

This work was carried out in collaboration among all authors. Author KNA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MMA and MME managed the analyses of the study. Authors HKK and AME managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study aimed to compare between the effect of pharmacoinvasive strategy (PI)& primary percutaneous coronary intervention (P-PCI) according to PCI related delay (door to ballon) on the mortality and morbidity during in-hospital stay and after 30-day follow up. Moreover, left ventricular systolic function was assessed by two-dimensional echocardiography at cardiology department, Tanta University.

Patients and Methods: The study was conducted on 300 patients that were divided into 2 main groups. Group A consisted of patients had primary PCI as reperfusion therapy and further divided into three groups according to PCI related delay (door toballon). Group A1, PCI-related delay is ≤60 minute(92patients). Group A2, PCI-related delay is >60 to ≤ 90 minute. (54patients). Group A3, PCI-related delay is >90minute (78 patients). The second group (group B), include patients who under gopharmaco-invasive strategy, PCI within 24 hour after thrombolysis (76 patients). In

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the second group, coronary angiography was done immediately in cases of failed thrombolysis and for successful thrombolysis; coronary angiography was performed within 3 – 24 hours.
Results: During hospital stay, more patients in group A3 died than those of group B or group A1, A2 with no statistical significance. In addition, morepatients in group A3 showed heart failure symptoms with statistical significance than those of group B, A1 and A2. Bleeding complications occurred significantly more in group B. During follow up visits more patients in group A3 complained of heart failure symptoms with statistical significance than those of group B, A1, A2 patients.
Conclusion: Primary PCI without door to balloon time delay (≤90 minutes)was encouraged and had the best results on morbidity and mortality. Also, pharmacoinvasive strategy was encouraged as being better than primary PCI when door to balloon time showed marked delay(<90 minutes).

Keywords: Pharmaco-invasive strategy; primary PCI.

1. INTRODUCTION

ST elevation myocardial infarction (STEMI) is a clinical syndrome defined by characteristic symptoms of myocardial ischemia accompanied with persistent electrocardiographic STelevation and the subsequent release of biomarkers due to myocardial necrosis. The most common triggering event is the disruption ofan atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade, resulting in total obstruction of the coronary artery. The current definitive treatment for STEMI is reperfusiontherapy consisting of percutaneous coronary intervention and thrombolysis, as recommended by the American College ofCardiology Foundation/American Heart Association and theEuropean Society of Cardiology [1,2].

STEMI is often caused by complete obstruction of an arteryby a blood clot(thrombus). As soon as the coronary blood supplyis interrupted, heart muscle (Myocardium) begins to be damaged, andthe longer the blood supply is obstructed the greater the myocardialdamage. In animal models nearly half of potentially viablemyocardium is lost within 1 hour, and two-thirds lost within 3hours, of experimental coronary artery occlusion [3].

The objectives of treatment are to restore coronary blood supply flow (reperfusion) as soon as possible after the onset ofsymptoms of acute STEMI. Reperfusion can be occured bymechanical techniques (coronary angioplasty, thrombus extraction catheters, stenting) that are grouped under the overarching term"Primary percutaneous coronary intervention"(P-PCI), or by the useof fibrinolytic drugs that lyse the coronary thrombus [3,4].

Primary percutaneous coronary intervention (P-PCI) is therecommended reperfusion therapy rather than fibrinolysis, if performed within 90-120 minute from the first medical contact in anexpert 24/7 facility. If PCI cannot be performed within 90 to 120minute, then thrombolysis, preferably within 30 minutes of arrival at thehospital, is recommended. Fibrinolytic therapy is recommended inpatients without contraindications. The original studies supporting this view however compared primary-PCI with in-hospital fibrinolysis only [5,6].

An important subsequent development has beenpharmacoinvasive (PI) strategy (early fibrinolysis with rescue PCIiffibrinolytic fail and with subsequent earlyangiography/PCI following fibrinolytic success). Some data support pharmacoinvasive strategy as being equal or better than primaryPCI especially when door to balloon time show marked delay [7,8].

Other studies indicate that there is a direct relation betweeninfarct size and that mortality rates increase the longer it takes todeliver primary PCI. By inference any advantage of primary PCIover fibrinolysis may become attenuated the longer the PCIrelateddelay. Thus, pharmacoinvasive strategy can provide analternative strategy to primary PCI [9,10].

2. PATIENTS AND METHODS

2.1 Patients

This study was conducted at the department of cardiovascular medicine, Tanta University hospital, it was carried out on 300 patients diagnosed with acute STEMI. Patients were divided into two main groups according to the method of reperfusion they received.

Group A: included patients who underwent primary percutaneous coronary intervention strategy (224 patients). Then, they were divided into three categories according toPCI-related delay (Door to balloon).

Group A1: PCI-related delay (Door to baloon) was≤60 minute. (92 patients).**Group A2**: PCI-related delay (Door to baloon) was >60 to ≤ 90 minute. (54 patients). **Group A3**: PCI-related delay(Door to baloon) was > 90 minute. (78 patients)

Group B: included patients who underwentPCI within 24 hour after thrombolysis (pharmaco-invasive strategy). (76 patients)

Inclusion criteria: Patients presented within 12 hours of symptom onset withSTEMIand treated with primary PCI or pharmacoinvasive strategy.

Exclusion criteria:

- Patients with myocardial infarction (MI) refused the previous two methods of intervention.
- Patients with MI and late presentation (more than 12 hours of symptom onset).
- Patients with MI with non-obstructive coronary artery disease (MINOCA) as acute myocarditis excluded by coronary angiography.

2.2 Methods

All patients were subjected to the following:

1- An informed consent was taken from all participants.
2- **History taking:** including personal history, presence of risk factors, past cardiac history and history of any comorbidities.
3- **Clinical examination:** including vital signs, General examination on the abdomen, chest, head, neck, and both the upper and lower limbs and local cardiac examination.
4- 12 leads surface electrocardiography (ECG).
5- **Blood sampling:** Serum cardiac biomarkers, complete blood count, random blood sugar serum, urea & creatinine, lipid profile.
6- Reperfusion either throughprimary percutaneous intervention for Infarct related artery orthrough pharmacoinvasive technique:

In pharmacoinvasive technique, Percutaneous coronary intervention was performed either immediately after failure of thrombolytic therapy (rescue PCI) or within 3 -24 hours after criteria of successful thrombolysis (routine early angiography/PCI strategy).

7- **Echocardiography:** full two-dimensional (2D) and M mode echocardiographic study in the standard views (parasternal long axis, short axis, apical four and apical two chambers) was done to assess left ventricular (LV) systolic function, resting segmental wall motion abnormalities (RSWMA) and any mechanical complications.
8- The study compared between those groups in the acute stage during hospitalization of the patients according to the following: a- Clinical outcomes: major adverse cardiac events (MACE)as mortality, heart failure, re-infarction. Also, bleeding complication, neurological complication and contrast induced nephropathy. b- Angiographic findings(base line and final TIMI score andangiographic complications as dissection and perforation). c- LV systolic function assessment by echocardiography.
9- Short-term follow up after one month for: a- Clinical outcomes: major adverse cardiac events (MACE) as mortality, heart failure, re-infarction and cerebrovascular accidents. b- LV systolic function assessment by echocardiography.

2.3 Statistical Analysis of the Data

The analysis was calculated by SPSS version 25. The qualitative parameters were described by number of frequency and percentage while the quantitative variables were described by mean, standard deviation and range. In addition, the comparison of independent quantitative variables was calculated by Anova with Tukey test in post hoc analysis. However, comparison between two qualitative variables was done by Chi square, Fisher's exact fisher and Monte Carlo tests.

3. RESULTS

3.1 Comparison between the Study Groups According to the Demographic Data, Risk Factors and Clinical Presentation

Males represented 73.3% of patients, while females represented 26.6% of patient presented by STEMI with a ratio of 2.75:1. The age of the study population ranged from 28-88 years. In this

study 103 patients were diabetics, and 129 were hypertensive, while 138 were active smokers and 46 were addicts. In this study 186 of the study population presented by anterior STEMI in which left anterior descending (LAD) was the culprit lesion, 98 patients presented by inferior STEMI and 10 patients presented by lateral STEMI, 6 patients presented by isolated posterior STEMI. Also 224 patient in our study presented by Killip class Iwhile 39 patients presented by Killip class II and36 patients presented by Killip Class III, IV.

3.2 Comparison between the Study Groups according to In-Hospital Adverse Effects

Regarding in-hospital mortality: There was no significant differences between four groups.

Regarding congestive heart failure symptoms: There wasstatistically significant difference between the fourgroups with marked incidence of congestive heart failure (CHF) in group A3.

Bleeding complication showed statistically significant difference between the four groups with marked incidence in group B.

3.3 Comparison between the Study Groups According to Follow-Up Adverse Effects (30 Days)

During follow up visit, there were no statistically significant difference between groups regarding all-cause mortality.

But, there wasstatistically significant difference between the four groups regarding congestive heart failure with marked incidence of heart failure in group A3.

For the median ejection fraction during admission there wasstatistically significant difference between the fourgroups with marked decrease in systolic function in patients in group A3.

For assessment of left ventricular systolic functionafter one month there wasstatistically significant difference between the fourgroups with marked decrease in systolic function in patients in group A3.

Table 1. Comparison between the studied groups according to clinical presentation

		Group A1 N (%) N=92	Group A2 N (%) N=54	Group A3 N (%) N=78	Group B N (%) N=76	X^2	P Value
Killip	1	78 (84. 8 %)	38 (70%)	52 (66.7%)	57 (75%)	9.091	0.168
	2	7 (7. 6%)	9 (16.7%)	12 (15.4%)	11 (14.5%)		
	3 and 4	7 (7. 6%)	7 (13%)	**14 (17.9%)**	8 (10.5%)		
Location of MI	Anterior	63 (68.47%)	25 (46.2%)	48 (61. 53%)	50 (65.78%)	11.625	0.226
	Inferior	23 (25 %)	26(48.1%)	27 (34.61%)	22 (28.94%)		Calculated by Monte Carlo
	Laterl	3 (3.261%)	2 (3.704%)	3 (3.846%)	2 (2.631%)		
	Isolated posterior	3 (3.261%)	1 (1.852%)	0 (0%)	2 (2.631%)		

Table 2. Comparison between the study groups according to in-hospital adverse effects

		Group A1 N (%) N=92	Group A2 N (%) N=54	Group A3 N (%) N=78	Group B N (%) N=76	X^2	P Value
Mortality		4 (4.348%)	5 (9.259%)	10 (12.8%)	6 (7.895%)	4. 049	0. 256
Bleeding	Minorbleed	7 (7.6%)	7 (13%)	8 (10.3%)	17 (22.4%)	12. 95	0. 043*
	Majorbleed	2 (2.2%)	1 (1.9%)	2 (2.6%)	5 (6. 6%)		
Heart failure		10 (10.9%)	10 (18.5%)	23 (29.5%)	12 (15.8%)	10. 23	0. 017*
Cardiogenic shock		4 (4.348%)	4 (7.407%)	11(14.1%)	5 (6.579%)	5. 848	0. 119

Table 3. Comparison between the study groups according to follow-up adverse effects (30 days)

	Group A1 N (%) N=82	Group A2 N (%) N=44	Group A3 N (%) N= 58	Group B N (%) N=61	X^2	P Value
Follow up Mortality	2 (2. 4%)	3 (6. 8%)	5 (8. 6%)	4 (6. 6%)	2. 72	0. 5
Follow up HF	6 (7. 3%)	5 (11. 4%)	13 (22. 4%)	5 (8. 2%)	8. 6	0. 035*

Table 4. Comparison between the studied groups according to EF assessment by Echocardiography before discharge&during follow up and RSWMA and Dilated dimensions

	Group A1 mean±SD (range) N=92	Group A2 mean±SD (range) N=54	Group A3 mean±SD (range) N=78	Group B mean±SD (range) N=76	F	P Value	Post Hoc Test
ECHO (EF) %	46.48 ± 8.69 (30-66)	45.57 ± 9.9 (20-64)	40.52 ± 9.2 (20-68)	43.8 ± 9.5 (28-65)	6.844	<0. 001*	P1 0. 942 P2<0. 001* P3 0. 135 P4 0. 01* P5 0. 633 P6 0. 04*
Follow up EF%	50.92 ± 7.87 (35-66)	50.32 ± 10.589 (20-65)	44.4 ± 9.62 (18-68)	49.79 ± 9.1 (30-65)	6.57	<0. 001*	P1 0. 985 P2<0. 001* P3 0. 88 P4 0. 007* P5 0. 991 P6 0. 007*
	Group A1 N (%) N= 92	Group A2 N (%) N=54	Group A3 N (%) N=78	Group B N (%) N= 76	X^2		P Value
ECHO (RWMA)	87(87%)	49(90.7%)	71(91%)	66(86.8%)	1.183		0.75
ECHO (Dilated)	16(17.4%)	15(28.8%)	29(37. 2%)	11(14.5%)	13.95		0.003*

4. DISCUSSION

Males represented 73.3% of patients, while females represented 26.6% of patient presented by STEMI with a ratio of 2.75:1. The age of the study population ranged from 28-88 years.

A study conducted by *STREAM TRIA* [11] in which the ratio of males to females having MI was 4:1 in the study population. Also, this came in agreement with the American heart association statistical annual updated report by Mozaffarian et al. [12] that found that STEMI is more prevalent in men than women.

In this study 186 of the study population presented by anterior STEMI in which LAD was the culprit lesion (62%), 98 patients presented by inferior STEMI (32.6%) and 10 patients presented by lateral STEMI (3.3%),6 patients presented by isolated posterior STEMI (2%).Also 224 patient in our study presented by Killip class I (74.6%) while 39 patients (13%) presented by Killip class II and 36 patients (12%) presented by Killip Class III,IV.

This came in agreement by *STREAM trial* [11] in which the majority of cases presented by anterior STEMI and patients presenting by Killip class I represented then majority of their study population 94% of all patients.In the study conducted by Gershlick et al. [13] anterior STEMI represented about 47% of MI and Killip class I represented the majority of their study population.

Study groups were compared regarding base line TIMI flow in coronary angiography. In group B, treated with fibrinolytic agents (30.26%) of patients achieved TIMI 0,I flow. While (69.73%) of patients achieved either TIMI flow II, III. This result was due to use of thrombolytic therapy before undergoing coronary angiography.But as would be expected in group A,the majority of cases were TIMI 0 with percentage of 69.5%,70.3%,73,0% of cases in groups A1,A2,A3 respectively.After PCI, patency rates were high in all study groups with final TIMI III achieved in (91.3%) in group A1,(79.6%) in group A2,(70.5%) in group A3, (88.1%)in group B. With marked incidence of no-reflow in group A3 (7.6%) of cases.

In *STREAM trial,* [11] in the group treated by pharmacoinvasive technique most patients presented by base line TIMI III (58.5%)of cases, while in the group treated by primary PCI most patients achieved base line TIMI 0 (59.3%). But the final TIMI III flow was achieved similarly in the group treated by pharmacoinvasive technique and group treated by primary PCI 91% and 92% respectively. Also the study conducted by Gershlick et al. [13] initial TIMI III flow for group treated by primary PCI is 21.4% of patients. And 58.6% of patients treated by pharmacoinvasive strategy.While the final TIMI III

flow was 92.3% in group treated by primary PCI and 91.6% in patients treated by pharmacoinvasive strategy.

Also in *the FAST-MI trial* [14] initial TIMI III flow for group treated by primary PCI is 18% of patients. And 37% of patients treated by pharmacoinvasive technique. While the final TIMI III flow was 89% in group treated by primary PCI and 84% in patients treated by pharmacoinvasive strategy. Regarding in-hospital mortality: In group A1, 4 patients died during hospital stay (4.3%). In group A2, 5 patients (9.2%). In group A3, 10 patients (12.8%). And in group B 6 patients (7.8%) there were no significant differences between groups.

Congestive heart failure symptoms occurred in group A1, 10 patients (10.8%). In group A2, 10 patients (18.518%). In group A3, 21 patients (26.923%). And in group B, 12 patients (15.7%). There was statistically significant difference between the fourgroups with marked incidence of CHF in group A3.

Bleeding complication occurred more in the pharmacoinvasive arm compared with primary PCI arm, 17 patients (22.3%) had minimal & minor bleeding and 5 patients (6.5%) had major bleeding within group B. There wasstatistically significant difference between the fourgroupswith marked incidence inpharmacoinvasive strategy.

During follow up visit, there were no marked differences between groups regarding all-cause mortality. In group A1, 2 patients died (2.4%). In group A2, 3 patients (6.8%).In group A3, 4 patients(6.8%).And in group B, 4 patients (6.5%).

But, there weremarked differences between groups regarding congestive heart failure. In group A1, 6 patients(7.3%).In group A2, 5 patients(11.3%).In group A3, 11 patients(18.9%). And in group B, 5 patients(8.1%).There wasstatistically significant difference between the four groups due to marked incidence of heart failure ingroup A3.

In the study conducted by Gershlick et al. [13] compared outcome in patients treated with pharmacoinvasive therapy (PI)with primary PCI (P-PCI)according to PCI related delay(P-RD) andcategorized patients in three groups, first with PCI related delay≤55 minute, second with PCI related delay >55–97 minute and thirdgroup with PCI related delay >97 minute and compared them withthose undergoing pharmacoinvasive strategy.

Comparing death, congestive heart failure, cardiogenic shockand myocardial infarction in Pharmacoinvasive therapy withprimary PCI arms occurred in 10.6% versus 10.3% (≤55 minute); 13.9% versus 17.9% (>55–97 minute) and 13.5%versus 16.2% (>97 minute), respectively. For P-RD ≤55min, fewer events tended to occur with P-PCI than PI [13].

Conversely, as PCI-related delay (P-RD) increased to >55 minute, patients withPharmacoinvasive therapy had better outcomes than primary PCI (P-PCI), suggesting advantages with PI when P-RD delay [13].

This came in agreement with ***STREAM trial,*** [11] which compared outcomes in patients treated with pha1rmacoinvasive therapy or Primary PCI presenting within 3 hours after symptom onset, unable to undergo P-PCI within 1 hour. The primaryend point was a composite of death, shock, congestive heart failure, or reinfarction up to 30 days, The primary end pointoccurred in (12.4%) in the Pharmacoinvasive group and in (14.3%) in the primary PCI group. More intracranial hemorrhages occurred in the Pharmacoinvasive group than in the primary PCIgroup.

In the FAST-MI trial, [14] they assessed 5-year mortality in STEMI patients from the *French registry of Acute ST-elevation or non-ST elevation Myocardial Infarction* (FAST-MI) 2005 according to use and type of reperfusion therapy. Of 1492 STEMI patients with first call <12 hours from onset, 447 (30%) received fibrinolysis (66% pre-hospital; 97% with subsequent angiography, 84% with subsequent PCI), 583 (39%) had primary PCI and 462 (31%) received no reperfusion. There was a numerical excess of reinfarction, stroke, and ventricular fibrillation with the fibrinolytic-based strategy, and an excess of cardiogenic shock with primary PCI. However, none of the in-hospital complications differed significantly for the two reperfusion strategies. In the FAST-MI trial major bleeding complication occurred more with the primary PCI arm with no statistical difference. While in 5-year follow up, Five-year survival was high in patients who had received reperfusion therapy with either primary PCI, or a pharmaco-invasive approach, with approximately two-thirds of the patients receiving fibrinolytic treatment in the pre-hospital setting. As expected, patients who did not get reperfusion therapy had a much higher mortality. When comparing the two reperfusion strategies, the results achieved with the pharmaco-invasive approach were at least as good as those with an

intended primary PCI strategy. *Also, the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction(CAPTIM) trial,* [7] has told that prehospitalfibrinolytic therapy with the patients brought to PCI-capable centers and with one third undergoing rescue angioplasty, could do at least as well as primary PCI up to 5 years after the initial episode.

5. CONCLUSION

Primary PCIwithout door to balloon time delay (≤90 minutes) was encouraged and had thebest results on morbidity and mortality. But in our daily clinical practice pharmacoinvasive strategywas considered safe alternative to primary PCI. Especially, considering logistical issues and delay in the initiation ofmanagement and the results of our study supportedpharmacoinvasive strategy as being better than primary PCIwhen door to balloon time showed marked delay(>90 minutes).

6. LIMITATIONS OF THE STUDY

The study had some potential limitations such as; small sizeof study population, which was due to many factors, one of themthat not all patients were willing to the idea of follow up after onemonth, also a lot of cases came with late presentation after theaccepted window of thrombolytic therapy, others refused doingPCI at our center due to logistic or cultural issues.

In addition, many patients who received thrombolytic therapywith signs of successful reperfusion underwent coronaryangiography later on after discharge due to financial reasons.

Another limitation was the short period assigned for followup which didn't allow the appearance of results for mortality, reinfarction & re-hospitalization. The chosen period was one monthonly to prevent fallacies in the results because mostly after onemonth the patients underwent elective PCI for other coronarylesions so this may affect the results.

Also the use of Simpson's method, M-mode might not be ofthe same accuracy in assessment the global & regional LVsystolic function as the newest techniques such as speckletracking & strain and strain rate.

CONSENT

An informed consent was taken from all participants.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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