J Cardiovasc Disease Res., 2018; 9(1):28-31.
A Multifaceted Peer Reviewed Journal in the field of Cardiology
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Original Article

Primary PCI versus Pharmaco-Invasive Strategy in Patients with ST-Elevation Myocardial Infarction; a Randomized Clinical Study

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ABSTRACT

Background: It is debatable whether immediate fibrinolysis followed by timely coronary angiography, provides a clinical outcome similar to that with primary percutaneous coronary intervention (PPCI) early after acute ST-segment elevation myocardial infarction (STEMI). **Methods:** During period from December 2016 to June 2017, 60 patients with STEMI were randomly assigned to undergo either primary PCI (Group I) or immediate fibrinolysis (Group II) with subsequent coronary angiography with PCI within 3 to 24 hr later. The primary end point was a composite of all-cause death, re-infarction, and target-vessel revascularization, re-hospitalization for cardiac reasons, any stroke and major bleeding up to 30 days. **Results:** The primary endpoint was reported in 23% of patient who had PPCI versus 33% in those who had pharmaco-invasive strategy (RR= 0.7, 95% CI 0.31-1.58, P= 0.46). Delay time from symptom onset to each of the two reperfusion strategies was shorter in group II than group I (110 ± 27.5 versus 186.8 ± 16.6 mins respectively, P <0.001). No statistically significant differences in various components of in-hospital outcome were found between groups. **Conclusion:** Immediate fibrinolysis followed by coronary angiography 3-24 hr later resulted in similar short term outcome and earlier effective reperfusion in patients with STEMI compared to PPCI.

Key words: Fibrinolysis, PCI, Reperfusion, STEMI.

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Submission Date: 15-09-2017;
Revision Date: 04-10-2017;
Accepted Date: 12-10-2017.
DOI : 10.5530/jcdr.2018.1.7

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy in patients presenting with ST-segment elevation myocardial infarction (STEMI).[1] Because most STEMI patients initially present to hospitals without PCI capabilities, performing a PPCI in a timely fashion poses a significant logistic challenge in many healthcare systems across the world. Despite efforts to decrease transfer times, PCI related system delays remain substantial in many countries especially those economically burdened including Egypt.[2]

Unfortunately, these delays clearly have an unfavorable impact on morbidity and mortality,[3] therefore early fibrinolysis followed by timely angiography often provides a faster reperfusion option in many patients than transfer for standard primary PCI.[4]

Many contemporary clinical trials[5,6,7] demonstrated equivalency of early (3-12 hr) routine post-thrombolysis PCI to standard PPCI in patients with STEMI eligible for reperfusion.

In light of encouraging results of trials comparing these 2 management strategies for STEMI which could give those patients more flexible options for emergent reperfusion, we think that it may be of considerable interest to conduct a similar work at our institution.

METHODS

Study design

This prospective, randomized, parallel group, single center clinical study included 60 consecutive patients with STEMI who were admitted to the coronary care unit (CCU) at Benha University Hospital, Egypt in the period from December 2016 to June 2017. All patients were candidates for reperfusion therapy. We aimed primarily to compare in-hospital and short term outcome of primary PCI versus Pharmaco-invasive strategy (immediate fibrinolysis then coronary angiography with possible PCI within 3-24 hr later) for reperfusion in eligible patients with STEMI. Our institutional review board and ethics committee approved the performance of this research, and all patients signed a written informed consent. *Key inclusion criteria* were: patients of both genders aged 18 years or older with chest pain lasting more than 30 min, ST segment elevation in 2 contiguous leads of at least 1 mm except ≥ 2 mm in V2-3 or presumed new onset left bundle branch block (LBBB). Successful reperfusion after thrombolytic therapy in patients who underwent pharmaco-invasive strategy including: at least 50 % ST segment resolution in the lead with maximum elevation in baseline ECG, improvement of chest pain. While *key exclusion criteria* were: absolute contraindications for thrombolytic therapy, evidence of mechanical complications of MI including cardiogenic shock, non-cardiac condition limiting life expectance to less than 6 months, evidence of pre-existing multi-vessel disease not amenable for revascularization, evidence of pre-existing more than stage 2 chronic kidney disease (CKD) defined as creatinine clearance less than 60 ml/Kg/min, evidence of pre-existing peripheral vascular disease precluding rapid emergent vascular access, and patient refusal to give consent.

Study medications

Streptokinase was the fibrinolytic agent used in those scheduled for pharmaco-invasive strategy and was given in the standard dosing regimen (1.5 million unites infused over 60 min) and was combined with low molecular weight enoxaparin (30-mg intravenous bolus followed by subcutaneous injection of 1 mg per kilogram of body weight [0.75 mg per kilogram for patients ≥75 years of age] every 12 hr) except for patients 75 years of age or older, in whom the intravenous bolus was omitted. In patients who were scheduled for PPCI; clopidogrel in a 600-mg loading dose (300mg for patients ≥75 years of age) followed by 150 mg daily for one week, then 75mg daily for one year. In those scheduled for pharmaco-invasive strategy, clopidogrel in a loading dose 300 mg was given followed by 75 mg daily. Aspirin (150 to 325 mg) immediately followed by 75 mg daily was applied in all patients. Beta blockers and ACEIs were given to all patients.

Primary PCI

Un-fractionated heparin (UFH) of 10000 units' bolus dose was given after sheath insertion. The procedure was done according to the standard

technique for coronary angiography and PCI. Trans femoral approach was done in all patients using 6 Fr sheaths. Diagnostic coronary angiography was done to explore non-infarct related artery. XB or Judkin left guide catheters were used for lesions in the left system, while Judkin right catheters for lesions in right coronary artery (RCA). Thrombus aspiration and glycoproteins inhibitors (Eptifibatide or Tirofiban intracoronary bolus followed by intravenous infusion for 12 hr) were used in lesions with heavy thrombus burden and or impaired TIMI flow after the procedure. The operator determined the length and diameter of implanted stents. Sheaths were removed 4 hr post procedure.

Study protocol

After initial presentation and full clinical assessment, eligible patients were randomly allocated using simple 1:1 randomization into one of 2 groups based on the reperfusion strategy:

Group (I): Primary PCI.

Group (II): Pharmaco-invasive strategy (immediate fibrinolysis followed 3 to 24 hr later by coronary angiography and PCI). (Figure 1)

Study endpoint

The endpoint of the study was a 30-days composite of all-cause death, re-infarction, target-vessel revascularization, re-hospitalization for cardiac reasons, any stroke and major bleeding.

Statistical analysis

Data management and statistical analysis were done using SPSS software version 23. Numerical data was summarized as mean and standard deviation or median and range. Categorical data was summarized as numbers and percentages. Comparisons between the 2 groups as regard numerical variables were done using independent *t* test. For paired data, Wilcoxon signed rank test was used. For categorical data, comparisons between both groups were done using chi-square test or Fisher exact test whenever appropriate. Log rank test was used to compare Kaplan-Meier curves for each group. All P values were two-sided. *P* value less than 0.05 is considered statistically significant.

RESULTS

Study population

The mean age was 52.3±10.1 years (51.7 ±10.1, 52.9 ±1.6 years in group I and group II respectively, P= 0.63). Seventy eight percent were males, 32% had history of DM, 30% were hypertensives, 68% were smokers, 13% were obese, 11% had known dyslipidemia, 8% had family history of premature CAD, 20% had past history of diagnosed CAD and 16% had prior coronary interventions. Between groups analysis did not reveal statistically significant difference in these baseline clinical characteristics. (Table 1)

Target STEMI

Eighty two percent of study population had anterior STEMI, 13% had inferior STEMI and 5% had lateral STEMI. Between groups analysis showed no statistically significant difference between groups in distribution of STEMI location (90% in group I versus 73.3% in group II had anterior STEMI, 6.7% in group I versus 20% in group II had inferior STEMI and 3.3% in group I versus 6.7% in group II had lateral STEMI, P = 0.34 for all). (Figure 2)

Key time intervals

Total ischemic time (time from symptom onset to arterial sheath insertion in group I and time from symptom onset to start of Streptokinase infusion in group II) was significantly shorter in group II versus group I

Table 1: Baseline characteristics for study population

	Group I (N=30)		Group II (N=30)		P value
Age,years, mean±SD	51.7 ±10.1		52.9 ±10.6		0.637
Male gender, n (%)	26	(86.7)	21	(70)	0.117
HTN	10	(33.3)	8	(26.7)	0.573
DM	11	(36.7)	8	(26.7)	0.405
Smoking	22	(73.3)	19	(63.3)	0.405
Dyslipidemia	4	(13.3)	3	(10)	0.688
Obesity	3	(10)	5	(16.7)	0.706
FH of premature CAD	2	(6.7)	3	(10)	1
PH of IHD	5	(16.7)	7	(23.3)	0.519
PH of coronary interventions	6	(20)	4	(13.3)	0.488

CAD= Coronary artery disease, DM= Diabetes Mellitus, HTN= Hypertension, IHD= Ischemia heart disease, PH= Past history

Table 2: Components of primary endpoint at 30-days

	Group I N=30		Group II N=30		
	N	(%)	N	(%)	P value
Re-hospitalization	1	(3.3)	2	(6.7)	1
Re-infarction	1	(3.3)	0	(0.0)	1
Target-vessel revascularization	1	(3.3)	2	(6.7)	1
Major bleeding	1	(3.3)	2	(6.7)	1
Stroke	0	(0.0)	1	(3.3)	NA
Mortality	0	(0.0)	1	(3.3)	NA

NA= non-applicable

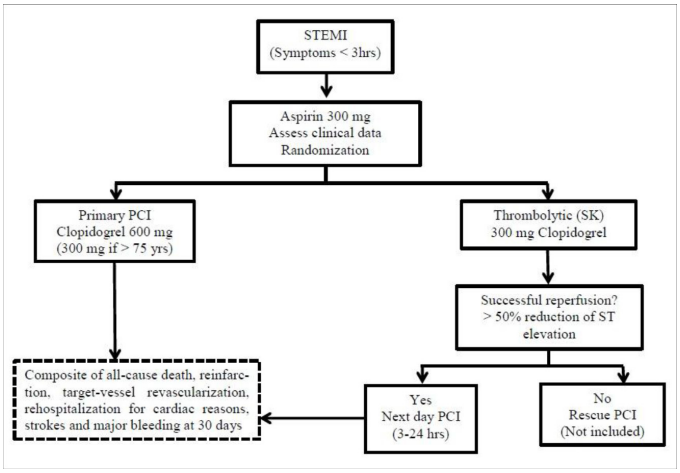

Figure 1: Flow chart of study protocol.

(186.8 ± 16.6 versus 110 ± 27.5 mins in group I and group II respectively, P <0.001). This was driven mainly by a shorter door to needle time in group II when compared to door to balloon time in group I (35 ± 7.9 versus 60 ± 10.5 mins in groups II and I respectively, P <0.001). Moreover, time

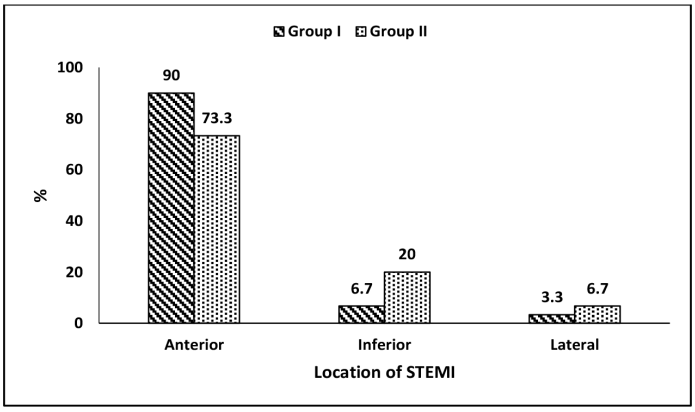

Figure 2: Location of STEMI in both groups.

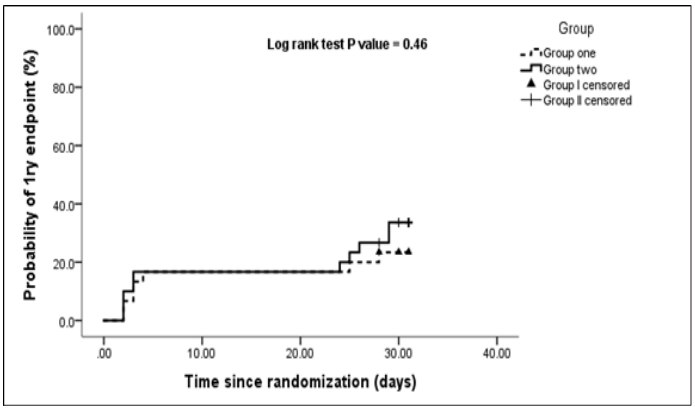

Figure 3: Kaplan-Meier curves for the primary endpoint.

interval from symptom onset to hospital admission was shorter in group II versus group I (75 ± 28.9 versus 126 ± 19 mins in groups II and I respectively, P <0.001).

Mean time delay before PCI in group II was 14.2 ± 6.8 hr.

Procedural details

The culprit vessel was found to be LAD in 90% of group I versus 70% of group II, P =0.053. No patients in group I had LCX as the culprit vessel versus 6.7% in group II. Seven percent in group I versus 13.3% in group II had RCA as the culprit vessel, P= 0.67) and Diagonal branch of LAD was found to be the culprit in 3.3% of both group I and II, P=1). There was significantly higher use of thrombectomy device in group I versus group II (27% versus 3% in group I and II respectively, P= 0.02). Glycoprotein IIb/IIIa antagonists were significantly used much more frequently in group I when compared to group II (40% versus 3% used GPIIb/IIIa antagonists in group I and group II respectively, P= 0.001).

Coronary stents during initial procedure were used more frequently in group II than group I (93% versus 73% of patients had coronary stent implanted in group II and group I respectively, P= 0.038). Regarding stent type, all stents used in group I were bare metal stents (BMS) but in group II, 79% used BMS and 21% used drug eluting stents (DES), P= 0.028 for all. Pre-dilatation was significantly used more frequently in group II than group I (56.7% versus 20% respectively, P= 0.003). Mean stent diameter was significantly higher in group II than group I (3.22 ± 0.42 versus 2.95 ± 0.28 mm respectively, P= 0.022) taking into account that there was no statistically significant difference between groups in the culprit vessel reference diameter (2.93 ±0.88 mm versus 3.01 ±0.91 mm in groups I and II respectively, P=0.74). Mean stent length was significantly longer in group II than group I (30 ± 6.5 versus 22.9 ± 6.2 mm respectively, P <0.001).

Of note, significantly more open vessels with TIMI-3 flow were found on first angiography before PCI in group II than in the group I.

In-hospital outcome

No patients in either group have experienced in-hospital strokes, reinfarction or emergency revascularization. One case of in-hospital mortality occurred in group I. Major bleeding was numerically higher in group I than group II (2 cases [7%] versus 1 case [3%]). Three cases (10%) experienced in-hospital heart failure in group I versus 4 cases (13%) in group II. All these components did not reach statistical significance when comparing both groups. Mean pre-discharge ejection fraction was significantly higher in group II than group I (52.3 ±6.2 versus 56.4 ±5.6% in group I and II respectively, P= 0.009).

Primary endpoint

The primary endpoint was reported in 23% of patients in group I 33% of patients in group II (HR= 0.7, 95% CI 0.31-1.58, P= 0.46). (Figure 3).

All individual components of the primary endpoint (except reinfarction) occurred more frequently in group II than group I but did not reach statistical significance. (Table 2).

DISCUSSION

In this study, similar clinical outcome was reported when comparing primary PCI and pharmaco-invasive strategy in patients with STEMI who were eligible for reperfusion.

This is reassuring, and provides some flexible options for emergent reperfusion for patients with STEMI who could not attain the guideline-recommended time frames for reperfusion due to local factors causing time delay which are very common in an economically burdened country like Egypt.

It is first useful and noteworthy to emphasize that findings of the present study should not be confused with the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) trial, which evaluated another fibrinolysis-based strategy for reperfusion i.e. facilitated PCI versus primary PCI. That study was prematurely terminated due to excess of strokes and early thrombotic complications when mandatory routine PCI within 1 to 3 hr after fibrinolysis was performed, regardless of evidence of successful reperfusion.[8] Our study was not designed to evaluate the facilitated strategy (that has been discouraged in recent guidelines)[1] and moreover, unlike the use of adjunctive therapies in our study, which were specified in the protocol, suboptimal use of adjunctive antithrombotic agents were reported in the ASSENT-4 PCI trial.

Our findings are supported by other trials in which lytic therapy was administered very early after symptom onset[9] and was combined with frequent additional revascularization.[10]

It's also important to reflect on our results in the context of GRACIA series of trials; GRACIA-1 trial demonstrated the appropriateness of an early post-thrombolysis interventional strategy when compared with an ischemia-guided conservative approach.[5] Three years later, GRACI-2 trial concluded that early (3-12 hr) routine post-thrombolysis reperfusion may be non-inferior to PPCI in limiting infarct size and preserving left ventricular function.[6] Recently, preliminary results of GRACIA-4 trial confirmed equivalency of early (3-12 hr) routine post-thrombolysis PCI to standard PPCI.[7]

Recently, a propensity score matched pooled analysis of more than 1400 patients comparing both reperfusion strategies in patients with STEMI

concluded that pharmaco-invasive strategy, compared with PPCI, yielded shorter time delay to reperfusion, higher culprit-vessel patency, and similar 12-month clinical outcome.[11]

As for our side, although both strategies for emergent reperfusion of STEMI appear equally effective in this study, we would recommend a pharmaco-invasive approach for our patients who could not undergo primary PCI in a timely fashion. This is based on many observations derived from our findings; [1] pharmaco-invasive strategy reduced the need for thrombectomy device which is costly in Egypt, [2] pharmaco-invasive strategy reduced the need to use GP IIb/IIIa antagonists which are expensive drugs and potentially hazardous as regard to enhanced bleeding risk, [3] pharmaco-invasive strategy allowed for achieving TIMI-3 flow more efficiently than primary PCI, [4] pharmaco-invasive strategy allowed the use of larger stent diameters (an observation that could have an impact on long term outcomes especially risk of stent thrombosis) and [5] because health administrative system in Egypt still do not easily compensate for DES use during primary PCI for reasons related to economic factors, we noticed that pharmaco-invasive strategy allowed some hours for patients and their families to seek different forms of insurance benefits for paid compensations for DES usage.

CONCLUSION

Immediate fibrinolysis followed by coronary angiography 3-24 hr later resulted in similar short term outcome in patients with STEMI when compared to primary PCI.

STUDY LIMITATIONS

1. Small sample size
2. Short follow up time.

CONFLICTS OF INTEREST

All authors disclose no conflicts of interest.

FUNDING

None.

ACKNOWLEDGEMENT

Authors would like to thank Dr. Mohamed Bendary for his great contribution to data analysis and all staff workers of coronary care unite at Benha University Hospital for their support.

ABBREVIATIONS USED

BMS: Bare metal stents; DES: Drug eluting stents; PPCI: Primary percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; SK= Streptokinase

SUMMARY

It's well known that PPCI is by far the best treatment option for patients with STEMI. Time delays remain a major obstacle for timely PPCI in economically burdened countries. Equivalency of early post-thrombolysis PCI to standard PPCI after STEMI has been demonstrated in many RCTs. This study reconfirms this fact and adds to the accumulating body of evidence supporting this approach giving those critically ill patients more flexible options for emergent reperfusion.

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Cite this article : Bendary A, Tawfek W, Mahros M, Salem M. Primary PCI Versus Pharmaco-Invasive Strategy in Patients with ST-Elevation Myocardial Infarction; a Randomized Clinical Study. J Cardiovasc Disease Res. 2018; 9(1):28-31.