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Original Article

Internal Medicine Section

Comparison of the Incidence of MACCE in Primary Percutaneous Coronary Intervention vs. Delayed Primary Percutaneous Coronary Intervention 24 hours After Taking Fibrinolytic Therapy in Patients with STEMI

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ABSTRACT

Introduction: Annually, over one million Percutaneous Coronary Interventions (PCIs) are performed worldwide. PCI is considered the most common procedure for revascularisation in patients with Coronary Artery Disease (CAD). Primary PCI (PPCI) is recognised as the best available option for the management of patients with ST-Segment Elevation Myocardial Infarction (STEMI). The most important issue about PCI is timing between symptoms' onset and performing intervention. In non-capable PPCI situations, fibrinolytic therapy alone or followed by angiography and intervention 2-24 hours after it, seems the best alternative choices, but delayed PCI's results >24 hours were also promising. The Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) include cardiac death, non-fatal myocardial infarction, cerebrovascular events and target vessel revascularisation.

Aim: To compare the occurrence of MACCE after PPCI and PCI >24 hour of successful fibrinolytic drugs.

Materials and Methods: The study was conducted among 457 patients with STEMI, admitted to Farshchian Heart Centre, Hamadan, Iran during 2013-2016. Ninety seven patients were managed with PPCI alone within 90 minutes of symptoms' onset and 360 patients took Reteplase within 30 minutes followed by PCI >24 hours of successful fibrinolytic therapy and were classified as control and case groups, respectively. Both groups evaluated for MACCE at 3, 6, 12, 24 and 36-month follow-up after PCI. Data analysis was performed with SPSS 18.0. Chi-square test and independent t-test used for analysis. All statistical analyses were carried out at 95% confidence level.

Results: Among 457 patients, 310 (67.8%) were male and 147 (32.2%) were female. There was no statistical significant difference in the occurrence of MACCE, including cardiac death (1% vs. 1.1%; p=0.946), non-fatal myocardial infarction (2.1% vs. 2.5%; p=0.803), target vessel revascularisation (5.6% vs. 8.2%; p=0.327), cerebrovascular complications (2.1% vs. 1.1; p=0.465), and total MACCE (13.4 vs. 10.3; p=0.382) between control group versus case group.

Conclusion: The incidence of MACCE between STEMI patients undergoing PPCI and those managed with fibrinolytic therapy followed by PCI >24 hours later was similar.

Keywords: Angioplasty, Coronary artery disease, Coronary reperfusion, Myocardial infarction

INTRODUCTION

Percutaneous Coronary Interventions (PCIs), which is the treatment of choice for CAD, has been increasingly performed over the past three decades [1]. PCI is the preferred method of revascularisation, except in the event of interventional non-compliance or inappropriate anatomy involvement, such as three-vessel disease or left main involvement requiring Coronary Artery Bypass Grafting (CABG) [2].

Fibrinolytic therapy is an alternative management strategy for patients diagnosed with STEMI, who are admitted to hospitals without PPCI capabilities on a full-time basis (24 hours a day/seven days a week) or centres lacking PCI facilities [3,4]. According to the most recent guidelines, when the estimated time for PCI exceeds 120 minutes, fibrinolytic therapy is the preferred method of treatment [5].

The MACCE include cardiac death, non-fatal Myocardial Infarction (MI), cerebrovascular events and target vessel revascularisation (TVR). MACCE is an appropriate indicator for long-term follow-up of STEMI patients managed with invasive strategy.

Clinical outcomes of patients which planned to be managed with fibrinolytic therapy followed by PCI is highly dependent on the time-related strategies [6]. As it is clear, PPCI is the best modality of treatments in the patients who presented with STEMI, but in non-capable PPCI centre, pharmacoinvasive strategy (fibrinolytic therapy followed by PCI 2-24 hours after) it seems to have similar clinical outcomes of mortality, reinfarction and Cerebrovascular Accidents (CVA) like PPCI [7-10].

Although the best timing for PCI following fibrinolysis is within 24 hours, but it seems delayed PCI (>24 hours of fibrinolytic therapy) results are also promising. Due to lack of adequate study in the comparison of PPCI with delayed PCI performed >24 hours after fibrinolytic therapy, thus the present authors aimed to compare MACCE following these two strategies.

MATERIALS AND METHODS

Study Design

This mixed cohort-study was performed among patients with acute STEMI, admitted to Farshchian Heart Centre, Hamadan, Iran, between 2013 and 2016. The patients were enrolled based on census sampling, which according to inclusion and exclusion criteria were 457 patients. The research protocol was approved by the Local Research Ethics Committee of Hamadan University of Medical sciences by letter number p/16/35/1/667. All the patients provided written informed consents.

Study Population

STEMI was defined as symptoms suggestive of AMI and ECG indicative of STEMI (ST segment elevation ≥2 mm in 2 contagious precordial leads or ≥1 mm in 2 contagious extremity leads or new left bundle branch block) and elevated cardiac enzymes (CK-MB or troponin I/T). Reperfusion therapy was administered to all eligible patients with STEMI, presenting with the symptoms within the past 12 hours. In this study, control group consisted of 97 patients undergoing PPCI, along with case group with 360 consecutive patients managed with fibrinolytic therapy followed by PCI >24 hours of it. Based on facilities' limitations, number of control group was lower than case group.

Decision for the management of STEMI patients was based on the hospital PCI capabilities, i.e., equipped catheterisation laboratories and presence of professional personnel and interventionists. Patients who were identified to benefit from PPCI were administered primary medications, including aspirin, clopidogrel and heparin and immediately transferred to Farshchian Heart Centre, Hamadan, Iran as tertiary centre (using clopidogrel other than anyother antiplatelet agents was based on available facilities). In other centres in Hamadan province without PCI capabilities and far from the present centre, STEMI patients were managed with fibrinolytics and then referred for the rest of management.

Inclusion Criteria

- Age 18-75 years,
- Symptoms implicate STEMI and ECG indicative of STEMI: ST segment elevation ≥2 mm in 2 contagious precordial leads or ≥1 mm in 2 contagious extremity leads or new left bundle branch block.

Exclusion Criteria

- >12 hours of symptoms onset,
- Non-ST segment Elevation- Acute Coronary Syndrome (NSTE-ACS) patients,
- Fibrinolytic medications other than Reteplase (such as Streptokinase),
- Antiplatelet medications other than Clopidogrel as second antiplatelet (such as Ticagrelor or Prasugrel),
- Associated Valvular heart disease,
- Associated chronic renal failure,
- Patients with Implantable Cardioverter-Defibrillator (ICD) or Cardiac Resynchronization Therapy (CRT),
- Patients managed by pharmacoinvasive strategy (underwent PCI 2-24 hours after taking fibrinolytic), facilitated strategy (fibrinolytic therapy which is followed by PCI immediately without successfulness consideration of fibrinolytic therapy) or managed by rescue PCI (mechanical reperfusion for failed fibrinolysis),
- Pregnancy,
- Coronary anatomy unsuitable for stent placement,
- Previous myocardial infarction in the area of the infarct-related vessel.

Primary End Points

The primary endpoint of this study was the occurrence of MACCE, including cardiac death, non-fatal MI, CVA, and TVR at 3, 6, 12, 24 and 36-month follow-ups in the clinic. TVR was defined as revascularization at the territory which was revascularised once before. "No reflow' phenomena was also investigated in two groups based on TIMI grade flow.

STATISTICAL ANALYSIS

Continuous data were presented as mean±SD and compared using Student t-test. Categorical variables were expressed as number and percentage and compared using chi-square test or Fisher's-exact test. All analyses were performed in SPSS version 18. The p-value <0.05 was considered significant.

RESULTS

Based on results shown in [Table/Fig-1], 43.1% of the patients were smokers, 25.7% were diabetic, 52.7% were hypertensive and 22.8% had high levels of Low-Density Lipoprotein (LDL). According to the analyses, both groups were comparable in terms of baseline characteristics and risk factors, except for age and Body Mass Index (BMI).

Variables		Overall	PPCI	PCI >24 h of successful fibrinolysis	p-value
Age, years			59.3±9.8	61.1±8.4	<0.001
Body mass index, kg/m^2			25.3±2.8	24.9±3	<0.001
Gender	Male	310 (67.8%)	69 (71.1%)	241 (66.9%)	0.404
	Female	147 (32.2%)	28 (28.9%)	119 (33.1%)	
Smoking	Never	260 (56.9%)	52 (53.6%)	208 (57.8%)	0.462
	Current user or positive history	197 (43.1%)	45 (46.4%)	152 (42.2%)	
Diabetes	No	340 (74.3%)	72 (74.2%)	268 (74.4%)	0.965
	Yes	117 (25.7%)	25 (25.8%)	92 (25.6%)	
Hypertension, mmHg	No	216 (47.3%)	39 (40.2%)	177 (49.2%)	0.117
	Yes	241 (52.7%)	58 (59.8%)	183 (50.8%)	
LDL, mg/dL	<100	353 (77.2%)	79 (81.4%)	274 (76.1%)	0.266
	≥100	104 (22.8%)	18 (18.6%)	86 (23.9%)	
Family history	Negative	360 (78.7%)	82(84.5%)	278 (77.2%)	0.118
	Positive	97 (21.2%)	15 (15.5%)	82 (22.8%)	

[Table/Fig-1]: Characteristics of patients.
PPCI: Primary percutaneous coronary intervention; LDL: Low-density lipoprotein

As shown in [Table/Fig-2], in the 36-month follow-up, 5 cases of cardiac death were reported : four cases from case group (1 after 12 months, 2 after 24 months and 1 after 36 months), and one case from control group (after 24 months); nevertheless, there was no significant difference between the groups (p=0.946). In addition, 11 patients were diagnosed with non-fatal MI; nine cases were managed by delayed PCI (1 after 6 months, 3 after 12 months,

Variables		PPCI	PCI >24 h of successful fibrinolysis	Total	p-value
		N (%)	N (%)	N (%)	
Cardiac death	Yes	1 (1%)	4 (1.1%)	5 (1.1%)	0.946
	No	96 (99%)	356 (98.9%)	452 (98.9%)	
Non-fatal MI	Yes	2 (2.1%)	9 (2.5%)	11 (2.4%)	0.803
	No	95 (97.9%)	351 (97.5%)	446 (97.6%)	
TVR PCI	Yes	2 (2.1%)	10 (2.8%)	12 (2.6%)	0.696
	No	95 (97.9%)	350 (97.2%)	445 (97.4%)	
TVR CABG	Yes	6 (6.2%)	10 (2.8%)	16 (3.5%)	0.105
	No	91 (93.8%)	350 (97.2%)	451 (96.5%)	
Cerebral complication	Yes	2 (2.1%)	4 (1.1%)	6 (1.3%)	0.465
	No	95 (97.9%)	356 (98.9%)	451 (98.7%)	
Total MACCE	Yes	13 (13.4%)	37 (10.3%)	50 (10.9%)	0.382
	No	84 (86.6%)	323 (89.7%)	407 (89.1%)	
Occlusion of vessel	Yes	2 (2.1%)	6 (1.7%)	8 (1.7%)	0.792
	No	95 (97.9%)	354 (98.3%)	449 (98.3%)	
No reflow	Yes	9 (9.3%)	6 (1.7%)	15 (3.3%)	<0.001
	No	88 (90.7%)	354 (98.3%)	442 (96.7%)	

[Table/Fig-2]: Outcome and follow-up.
PPCI: Primary percutaneous coronary intervention; MI: Myocardial infarction; TVR: Target vessel revascularization; CABG: Coronary artery bypass surgery; MACCE: Major adverse cardiovascular events

4 after 24 months and 1 after 36 months) and two by primary PCI (both after 24 months) (p=0.803). Moreover, 28 patients required TVR (20 cases from case group (1 after 3 months, 4 after 6 months, 5 after 12 months, 7 after 24 months, 3 after 36 months) and eight cases after control group (2 after 6 months, 2 after 12 months, 3 after 24 months, 1 after 36 months)); the management results were similar to these patients (p=0.327).

Furthermore, six patients developed cerebrovascular complications (four after delayed PCI (2 after 6 months, 1 after 12 months and 1 after 24 months) and two after primary PCI (1 after 12 months and 1 after 24 months) (p=0.465).

Based on the results, there was no significant difference in the incidence of MACCE between the two groups. The only significant difference was attributed to the "no-reflow phenomenon", which occurred more commonly in the control group (p<0.001).

DISCUSSION

In the present study, MACCE was compared between two groups of patients with STEMI, who were either managed by PPCI or delayed PCI >24 hours of successful fibrinolytic therapy. No significant difference was found in the occurrence of MACCE after PPCI and delayed PCI following fibrinolytic therapy.

Facilitated PCI refers to fibrinolytic therapy, immediately followed by PCI without any consideration for the success of fibrinolytic therapy [11]. According to many clinical trials, not only facilitated PCI is superior to PPCI, it is associated with higher rates of mortality and morbidity [12,13]. In a review study by Keeley EC et al., on patients receiving facilitated or PPCI, the rates of mortality, MACCE, major bleeding, total CVA and haemorrhagic CVA were significantly higher in the facilitated PCI group [14]. Pharmacoinvasive strategy refers to routine PCI, performed 2 to 24 hours following fibrinolytic therapy [15]. Several studies have reported similar outcomes for the pharmacoinvasive strategy and PCI in patients with STEMI [7,16]. According to the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) guidelines (2013), indications for coronary angiography 2 to 24 hours after successful fibrinolytic therapy in stable patients (before discharge) are categorised as Class IIA with level B evidence [3]. There is some evidence suggesting that early PCI after fibrinolytic therapy reduces the risk of ischaemic complications and no-reflow phenomenon [17,18]. Also, some studies have reported shorter and more complete reperfusion after pharmacoinvasive strategy, compared to PPCI [19,20].

According to the present study, clinical outcomes of performing PCI after >24 hours of successful fibrinolytic therapy were promising. Few clinical trials investigated this issue. Based on 2013 ACCF/AHA guideline for the management of patients with STEMI, indication for PCI of an infarct artery for stable patients >24 hours of successful fibrinolysis, is classified as IIB, but delayed PCI of a totally occluded infarct artery >24 hours after STEMI is III [3]. Study performed by TIMI patients, which compared invasive strategy (routine angiography followed by PCI 18-48 hours after successful fibrinolysis with recombinant tissue Plasminogen Activator (rtPA)) with conservative strategy (PCI only performed for patients with spontaneous or exercise-induced ischaemia) showed similar rates of reinfarction and death within 42 days [21]. "Should We Intervene Following Thrombolysis?" (SWIFT) Trial Study Group investigated clinical outcomes of patients with acute MI which managed with fibrinolytic therapy with Anistreplase followed by angiography and intervention as needed (intervention group) or with fibrinolytic therapy followed by conventional care (conventional group). There was no statistically significant difference between two groups in occurrence of mortality, reinfarction and bleeding complications after one year follow-up [22]. In a study published by Di Pasquale et al., clinical outcomes including ejection fraction, ischaemic events, restenosis and bleeding of delayed PCI >12-72 hours of successful fibrinolysis were promising [23]. Another clinical trial which somehow support the efficiency of this strategy is the study which was conducted by Gupta M el al., [24]. They demonstrated that in hospital revascularisation following successful fibrinolytic therapy for acute MI patients resulted in decreased rates of reinfarction, recurrent ischaemia and improved survival at one month and one year follow-up, but the optimised timing for PCI has not been mentioned [24].

LIMITATION

The sample size for the patients managed with PCI was less because of limitations of the facility where the study was conducted. However, the strength of the study is the long-term follow-up of patients.

CONCLUSION

The present study showed no significant difference in terms of the occurrence of MACCE (including cardiac death, non-fatal myocardial infarction, cerebrovascular events and need of TVR with PCI or CABG) between PPCI and delayed PCI 24-hours after fibrinolytic therapy (before discharge). Based on the findings, the "no-reflow" phenomenon was significantly more common in the control group compared to case group.

Overall, in the absence of PPCI capabilities, delayed PCI after 24 hours of taking fibrinolytic therapy is a proper alternative treatment for STEMI patients. However, further studies are recommended with larger sample sizes to examine the efficacy of this strategy.

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