



The effect of intracoronary versus intralesional injection of eptifibatide on myocardial perfusion outcomes during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction; A randomized clinical trial study

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Original Article

Abstract

BACKGROUND: Previous studies have proved that intracoronary injection of eptifibatide is safe and more effective in infarct size reduction and clinical outcomes than intravenously injection in the patients with acute myocardial infarction (AMI). This study aimed to compare the effect of localized and intracoronary injection of eptifibatide on myocardial perfusion improvement and its outcomes.

METHODS: We conducted a randomized clinical trial study of 60 patients presented with thrombotic AMI. The patients underwent percutaneous coronary intervention (PCI), and were randomly divided into two equal number groups. The first group received two bolus doses of 180 µg/kg eptifibatide through guiding catheter. The second group received the same bolus doses through export aspiration catheter into the coronary lesion directly. Thrombolysis in myocardial infarction (TIMI) flow, myocardial blush grade (MBG), and no-reflow phenomenon were primary end points. Secondary end points were pre- and postprocedure cardiac arrhythmia, in-hospital mortality, adverse effects, reinfection, pre-discharge ventricular systolic function, and re-hospitalization and mortality after 6 month of follow up.

RESULTS: The mean ages of group I and group II were 58.3 ± 1.8 and 57.0 ± 2.0 years, respectively, and most of patient were men (90% in group I and 80% in group II). Postprocedural TIMI flow grade 3 was achieved in 60.0% and 76.7% of the intracoronary and intralesional groups, respectively (P = 0.307). Postprocedural MBG grade 3 was achieved in 53.3% and 70.0% in intracoronary and intralesional groups, respectively (P = 0.479). There was no significant difference between the groups in no-reflow assessment. Moreover, no significant difference was seen between the two groups in secondary end-point analysis.

CONCLUSION: Both methods of intracoronary and intralesional eptifibatide administration during primary PCI in patients with acute ST-elevation myocardial infarction (STEMI) were safe and similar in myocardial perfusion outcomes.

Keywords: Myocardial Perfusion Imaging, Eptifibatide, Myocardial Infarction

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Introduction

Primary percutaneous coronary intervention (PCI) is the standard treatment for patients with acute myocardial infarction (AMI).¹ Embolism, thrombus and vascular debris toward the distal vascular bed may occur during PCI which impairs myocardial perfusion, and thus aggravates clinical outcomes.²

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Furthermore, microvascular occlusion can occur in the large proportion of patients that undergoing successful PCI which will be associated with increased infarct size, reduced ventricular systolic function, and increased mortality.³

In order to prevent and treat distal embolization and improve myocardial perfusion, the specialists can use mechanical and/or pharmacological intervention methods that will improve clinical outcomes in patients with ST-elevation myocardial infarction (STEMI).^{4,5} As a conventional method, glycoprotein (GP) inhibitors injection into infarcted vessels will increase drug concentration dramatically, and thus reduces available GP IIb/IIIa receptors to bind to fibrinogens in the microvessels.⁶

Previous studies have proved that intracoronary injection of eptifibatide (as a GP IIb/IIIa receptors inhibitor) is more effective in reduction of infarct size and clinical outcomes without significant increase in major bleeding than intravenous injection in the patients with AMI.⁵⁻⁷ As a novelty, we hypothesized that intralesional eptifibatide injection could be more effective than intracoronary injection, because drug infusion through guiding catheter (situated in the left main or right coronary artery) causes drug back flow to the aorta and simultaneous drug entry into the normal vessels. So, the aim of our study was to compare eptifibatide localized and intracoronary injection on myocardial perfusion improvement and its outcomes.

Materials and Methods

Study participants and design: This was a randomized clinical trial study reviewed and approved by the research ethics committees in Isfahan University of Medical Sciences, Isfahan, Iran, and registered by the Iranian Registry of Clinical Trials (IRCT number: IRCT2016122722134N4). All patients gave written informed consent to participate in the study. A total of 160 patients with AMI diagnosis who presented to Shahid Chamran Heart Center (Isfahan, Iran) were selected.

Inclusion criterion was diagnosis of STEMI as defined by chest pain suggestive for myocardial ischemia for at least 30 minutes before hospital admission, and symptoms onset time less than 12 hours with 1 mm ST-segment elevation in 2 or more contiguous leads (for V1-V3, ST elevation was 2 mm) simultaneously. These patients should also have thrombus burden grade three or more on the angiography. Thrombus burden (TB) was graded (G) as G0 = no thrombus, G1 = possible thrombus, G2 = small (greatest dimension \leq 1/2 vessel

diameter), G3 = moderate ($>$ 1/2 but $<$ 2 vessel diameter), G4 = large (\geq 2 vessel diameter), G5 = unable to assess TB due to vessel occlusion.⁸ Diagnosis and patient management was done by three specified interventional cardiologists.

Presenting with STEMI more than 12 hours of symptom onset, rescue PCI after thrombolytic therapy, with contraindications for antiplatelets such as bleeding disorder including hematuria, gastrointestinal bleeding, or known any bleeding tendency, recent stroke (less than 6 months), thrombocytopenia (platelet count $<$ 100.000/cm³), and cardiogenic shock were considered as exclusion criteria.

Finally, 97 patients were excluded and 63 patients were selected for coronary intervention. The patients were randomized in two groups by specified on-call interventional cardiologists via using random number table method. In group I (intracoronary administration group, n = 32), patients received two bolus doses of eptifibatide through the guiding catheter in the infarct-related artery. In group II or intralesional administration group (n = 31), boluses of eptifibatide were administered through the export aspiration catheter into the lesion of infarct-related artery. These treatment methods were safe, and would not put the patient at higher risk (Figure 1).

Treatment: Standard therapy for all patients with pain reduction (analgesics and/or intravenous nitroglycerin), decreasing oxygen demand (beta-blocker), statin therapy, antithrombotic medications including 325 mg of acetylsalicylic acid, a 600 mg loading dose of clopidogrel, and heparin therapy after electrocardiographic confirmation of STEMI, were done usually in the emergency department. All the patients were transferred to the catheterization laboratory quickly. During PCI, when the wire had crossed the occlusion, the initial treatment step consisted of manual thrombus aspiration (Export aspiration catheter, Medtronic Inc., Santa Rosa, USA) in both groups. Over a period of 1 minute after the thrombus aspiration, in the intracoronary group, two separated bolus doses of eptifibatide with a 5-minute interval (each 180 μ g/kg) were administered through the guiding catheter. The same doses of medication were administered through the export aspiration catheter into the lesion of infarct-related artery. Additional pre- or post-intervention dilatation with a balloon might be required in certain patients.

After the PCI, treatment included aspirin (80 mg), clopidogrel (75 mg), beta-blockers, lipid-lowering agents, and angiotensin converting enzyme (ACE)-inhibitors or angiotensin II receptor blocker.

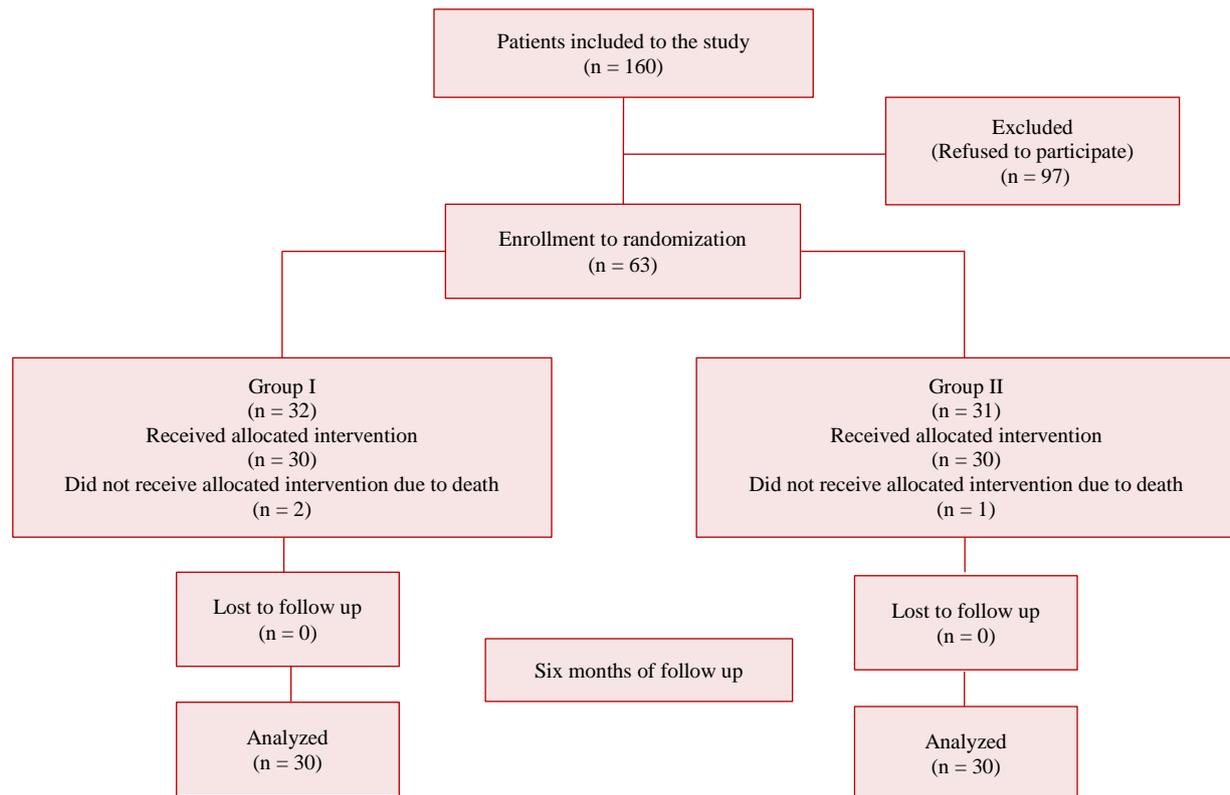


Figure 1. Consort diagram

The primary end points were postprocedural assessment of thrombolysis in myocardial infarction (TIMI) flow, myocardial blush grade (MBG), and no-reflow phenomenon. TIMI flow grade of less than 2, and MBG of less than 2 were described as angiographic no-reflow. These parameters were evaluated by another cardiology interventionist who was blinded to the groups. Secondary end points were pre- and postprocedure cardiac arrhythmia, in-hospital mortality, adverse effects including hemorrhage and stroke, reinfection, global ventricular systolic function (measured by conventional transthoracic echocardiography) before discharge, and re-hospitalization and mortality after 6 months of follow up. Follow-up information would be obtained from hospital records as well as by telephone interviews with the patients.

Statistical analyses: All statistical analysis was conducted on intention to treat basis by using the statistical program for social science (SPSS) software (version 15.0, SPSS Inc., Chicago, IL, USA). Statistician was blind to treatment condition.

Continues and categorical variables were reported as mean \pm standard deviation (SD) and absolute number (percent). Pearson's chi-square or fisher's exact test (if needed) and Student's t test

were used for comparison categorical and continues variables between groups, respectively. All differences were considered as statistically significant at a P value of less than 0.050.

Results

Finally, sixty patients including two equal group were analyzed. Baseline demographic and clinical characteristics are presented in table 1. There was no significant difference between groups in demographic, clinical, and drugs variables ($P > 0.050$ for all).

No significant difference was between the two groups on AMI level, culprit vessel, and severity of coronary artery diseases (CAD) ($P > 0.050$ for all). In both groups, the most common MI level (63.3%) was inferior MI, and the most common artery involvement (approximately 60.0%) was right coronary artery (Table 2).

Table 3 shows the frequency distribution of arrhythmia before the procedure, and the incidence of AMI and mortality after the PCI. There was not any significant difference in arrhythmia incidence between the two groups ($P = 0.228$). However, the frequency of cardiac arrhythmia in the group I (5 patients) was more than group II (2 patients).

Table 1. Baseline demographic and clinical characteristics for each group

Variables	Group I (n = 30)	Group II (n = 30)	P
	[n (%)]	[n (%)]	
Gender (man)	27 (90.0)	24 (80.0)	0.620
History of IHD	5 (16.6)	4 (13.3)	0.802
Diabetes mellitus	7 (23.3)	9 (30.0)	0.506
Hypertension	5 (16.7)	10 (33.3)	0.136
Current smoker	13 (43.3)	14 (46.6)	0.703
Cardiac drug consumption			
Aspirin	6 (20.0)	13 (43.3)	0.052
Clopidogrel	1 (3.3)	1 (3.3)	0.981
Statin	3 (10.0)	12 (40.0)	0.052
Beta-blocker	4 (13.3)	5 (16.6)	0.676
ACEI or ARB	2 (6.6)	7 (23.3)	0.062
	Mean ± SD	Mean ± SD	
Age	58.3 ± 1.80	57.0 ± 2.05	0.091

IHD: Ischemic heart disease; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; SD: Standard deviation

It should be noted that the frequency of cardiac arrhythmia during the hospitalization was only one person (3.3%) in the intracoronary group, and no patient in the intralesional group ($P = 0.310$). Remarkably, the incidence of mortality during the hospitalization was very low and not significant ($P = 0.554$). The incidence of bleeding and stroke after PCI were very low in both groups including 3.3% in group II (only one case with cerebral stroke and no case of bleeding), and 6.7% in group I (one case of gastrointestinal bleeding and one case of cerebral stroke) ($P = 0.554$).

After six month of follow up, mortality rate was one patient (from group II) ($P = 0.312$). Two members of group II and one member of group I had to be re-hospitalized ($P = 0.554$). Figure 2 shows the bar graph of the percentage of cardiac

events six months after PCI. No MI was seen among the patients of both groups.

There was no significant difference between the two groups in global ventricular systolic function assessment (38.80 ± 2.68 vs 41.00 ± 3.65 percent in group I and II, respectively; $P = 0.440$).

Table 4 shows the postprocedural TIMI flow, coronary MBG of infarct-related artery, and no-reflow phenomenon incidence. Postprocedural TIMI flow grade 3 was achieved in 60.0% and 76.7% of the intracoronary and intralesional groups, respectively ($P = 0.307$). Postprocedural MBG grade 3 was achieved in 53.3% and 70.0% of groups I and II, respectively ($P = 0.479$). About no-reflow phenomenon, there was no significant difference between the groups according to both methods of TIMI flow and MBG ($P = 0.071$) (Table 4).

Table 2. The comparison of frequency distribution of myocardial infarction (MI) level, culprit vessels, and severity of coronary artery diseases (CAD) between the groups.

Variables	Group I (n = 30)	Group II (n = 30)	P
	[n (%)]	[n (%)]	
AMI level			> 0.999
Inferior ± lateral/posterior	19 (63.3)	11 (36.6)	
Anterior ± septal/lateral	19 (63.3)	11 (36.6)	
Culprit vessels			0.570
LAD	11 (36.6)	11 (36.6)	
LCX	1 (3.3)	0 (0.0)	
RCA	18 (60.0)	19 (63.3)	
Severity of CAD			0.525
1-vessel disease	16 (53.3)	13 (43.3)	
2-vessel disease	9 (30.0)	12 (40.0)	
3-vessel disease	5 (16.6)	5 (16.6)	

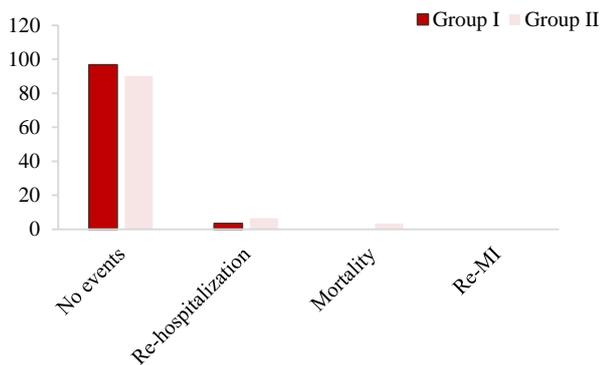
AMI: Acute myocardial infarction; LAD: Left anterior descending artery; LCX: Left circumflex artery; RCA: Right coronary artery; CAD: Coronary artery diseases

Table 3. The comparison of frequency distribution of preprocedural cardiac arrhythmia, postprocedural acute myocardial infarction (MI), and in-hospital mortality.

Variables	Group I (n = 30)	Group II (n = 30)	P
	[n (%)]	[n (%)]	
Cardiac arrhythmia (preprocedural)	5 (16.6)	2 (6.6)	0.228
Acute MI (postprocedural)	1 (3.3)	1 (3.3)	0.957
In-hospital mortality	2 (6.6)	1 (3.3)	0.554

MI: Myocardial infarction

However, the results were better in group II in terms of TIMI flow, MBG, and no-reflow phenomenon.

**Figure 2.** The bar graph showing percentage of cardiac events, after six month follow up

MI: Myocardial infarction

Discussion

The finding of this study showed that both methods of intracoronary and intralésional eptifibatid administration during the primary PCI in patients with acute STEMI were safe and similar in myocardial perfusion outcomes. In this study, PCI outcomes and myocardial perfusion were evaluated

by TIMI flow and coronary MBG grading. Cardiac arrhythmia, in-hospital mortality, adverse effects, and pre-discharge left ventricular (LV) function were also similar in both groups.

Several studies have shown that intracoronary injection of glycoprotein GP IIb/IIIa inhibitors (in comparison with systematic injection) increases drug local concentration at the site of thrombosis and infarcted vessels.⁹⁻¹² Increased intra-coronary concentrations of GP IIb/IIIa inhibitors, such as abciximab, was safe and effective in infarct size reduction and myocardial perfusion (TIMI flow) improvement.⁶ Deibele et al. reported that intracoronary eptifibatid administration during PCI in patients with acute coronary syndromes was accompany with higher occupancy of local platelet glycoprotein IIb/IIIa receptor, which was associated with improved microvascular perfusion.¹⁰ Gu et al. studied about the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of STEMI. They concluded that intracoronary abciximab injection through guiding catheter was associated with myocardial perfusion improvement which was evaluated by myocardial blush grade.¹¹ In addition, Hamza et al.¹² studied 75 patients with acute MI and coronary thrombosis who had angioplasty with stenting.

Table 4. The comparison of postprocedural thrombolysis in myocardial infarction (TIMI)-flow, coronary myocardial blush grade (MBG), and no-reflow phenomenon between the groups

Variables	Group I (n = 30)	Group II (n = 30)	P
	[n (%)]	[n (%)]	
TIMI flow			0.307
Grade 0	1 (3.3)	0 (0.0)	
Grade 1	6 (20.0)	2 (6.7)	
Grade 2	5 (16.7)	5 (16.7)	
Grade 3	18 (60.0)	23 (76.7)	
Coronary MBG			0.479
Grade 0	1 (3.3)	0 (0.0)	
Grade 1	5 (16.7)	4 (13.3)	
Grade 2	8 (26.7)	5 (16.7)	
Grade 3	16 (53.3)	21 (70.0)	
No-reflow (Coronary MBG)	6 (20.0)	4 (13.3)	0.071
No-reflow (TIMI flow)	7 (23.3)	2 (6.7)	

TIMI: Thrombolysis in myocardial infarction; MBG: Myocardial blush grade

In comparison to intracoronary eptifibatide administration and mechanical aspiration, pharmaceutical therapy had significantly better results in terms of MBG and corrected TIMI frame count.¹² The same results also were seen about the effectiveness and safety of intracoronary administration of GP IIb/IIIa inhibitors (lower bleeding risk) by Stone et al.¹³ and Hassan et al.¹⁴

In contrast to those studies, researches on comparison of intracoronary and intralesional injection of GP IIb/IIIa inhibitors are fewer.¹⁵⁻¹⁷ In a case report by Dziejewicz et al., intralesional infusion of abciximab using a dedicated therapeutic perfusion catheter accompanied with increased concentrations of abciximab at the culprit lesion and in the distal vascular bed and finally, optimal clinical results.¹⁵ In another trial by Stone et al., it was shown that intralesional abciximab and thrombus aspiration may have long-term benefits in patients with anterior STEMI in regard to mortality and ischemic events.¹⁶ Prati et al. indicated that local intracoronary administration of abciximab by means of a dedicated perfusion catheter reduced thrombus burden, improved coronary microcirculation (shorter TIMI frame count), and tended to lower procedure-related MI and major adverse cardiac event (MACE) after 1 year of follow up in comparison to intracoronary drug delivery.¹⁷ In our study, there was no significant difference between the intracoronary and intralesional group in terms of TIMI flow grade, MBG, no-reflow phenomenon, and clinical outcomes; however, the intralesional eptifibatide injection had better results.

The small number sample size and shorter follow-up period in comparison to previous studies were some limitations of this study. It is recommended to make further studies with more groups with comparison of systemic, intracoronary, and intralesional administration of GP IIb/IIIa inhibitors.

Conclusion

The results of this study indicates that intracoronary and intralesional administration of eptifibatide during primary PCI in patients with acute STEMI are safe, and have similar outcomes regarding myocardial perfusion evaluated by TIMI flow and coronary MBG grading. Cardiac arrhythmia, in-hospital mortality, adverse effects, and pre-discharge LV function were also similar in both groups.

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Conflict of Interests

Authors have no conflict of interests.

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