Intracoronary Versus Intravenous Administration of Eptifibatide During Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes

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Abstract- Platelet activation and aggregation play a major role in thrombosis formation of coronary arteries in patients with Acute Coronary Syndrome (ACS) and is responsible for most ischemic complications during PCI. There is little information on the benefits and side effects of intracoronary and intravenous injection of Eptifibatide, a potent antiplatelet agent; therefore, this study was performed with the aim to compare coronary blood flow velocity by measurement of TIMI frame count. In intravenous versus intracoronary bolus administration of Eptifibatide during PCI in ACS patients. This non-randomized clinical trial study was performed on 103 patients with acute coronary syndromes who referred to the cardiac emergency ward of Ghaem hospital, Mashhad University of Medical Sciences, and were candidates for urgent coronary angiography and PCI. Forty-eight cases received intracoronary bolus Eptifibatide and 55 intravenous Eptifibatide. TIMI Frame Count and Corrected TIMI Frame Count were used to comparing the effect of these two methods on coronary blood flow velocity. Data were analyzed by SPSS software (version 22). To compare the quantitative variables in the two groups, according to the distribution of variables, the *t*-test was used if it was normal or the Mann-Whitney test was used if it was not normal. A *Chi*-square test was also used to compare qualitative variables into two groups. $P<0.05$ was considered statistically significant. Mean of age, gender, and cardiovascular risk factors were similar in the two groups. There was no significant difference in terms of serum Creatine Kinase MB (CKMB) level, Left Ventricular Ejection Fraction (LVEF), coronary artery lesion length, coronary artery diameter, coronary thrombosis, and coronary artery thrombectomy in two groups. Based on Student's t-test, there was no significant difference between mean TIMI Frame Count in different coronary arteries in the intracoronary and intravenous injection groups (In LAD, $P=0.518$; For LCX, $P=0.576$; and in RCA, $P=0.964$). The complications were observed in 11 patients (22.9%) of the intracoronary injection group and 9 (16.4%) of the intravenous injection group; the difference was not significant ($P=0.402$). The effects and complications of Eptifibatide were not significantly different in Intracoronary and intravenous administration in ACS patients during PCI and at the time of patients' hospitalization.

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Keywords: Acute coronary syndrome (ACS); Percutaneous coronary intervention (PCI); Eptifibatide; Intracoronary; Intravenous; Thrombolysis in myocardial infarction (TIMI); TIMI frame count; Corrected TIMI frame count; Major cardiac adverse events (MACE)

Introduction

Platelet activation and aggregation, which have a major role in thrombosis formation in coronary arteries,

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are responsible for most ischemic complications during PCI (1). More potent antiplatelet drugs are used in ACS patients, especially those undergoing PCI. In many recent studies, antiplatelet agents with different doses have been used with different combinations to prevent further thromboembolic events in these patients (2,3).

Recently, in patients with the acute coronary syndrome who were at high risk for cardiovascular events, instead of clopidogrel, more powerful and effective drugs such as Prasugrel or Ticagrelor have been used. Over the past decade, several clinical studies have shown that the combination of intravenous injection of Glycoprotein IIb/IIIa inhibitors with LMWH (Low Molecular Weight Heparin) or Unfractionated Heparin leads to a reduction in ischemic cardiac complications compared with heparin alone during PCI (4).

Eptifibatide is a small-molecule glycoprotein IIb/IIIa inhibitor, which is commonly used in this class of drugs. It has a rapid onset and offset of action, and the current dosing for eptifibatide was derived from pharmacokinetic studies assessing the need to obtain adequate (>80%) and persistent inhibition of platelet aggregation (5-7). Eptifibatide is widely used in PCI settings for patients with ACS, and changes in dosage and routes of its administration have gained attention to decrease the adverse reactions and maximize the antiplatelet effect of the drug (8,9).

Deibele *et al.,* in a study, showed that intracoronary eptifibatide regimen was associated with higher local platelet IIb–IIIa receptor occupancy and improved microvascular perfusion compared to intravenous bolus injection among patients undergoing PCI for acute coronary syndromes. These researchers also suggested that intracoronary administration might reduce the bulk of microemboli (10).

Also, Soon *et al*., have evaluated the outcomes of intracoronary bolus versus intracoronary bolus plus intravenous infusion eptifibatide in primary PCI patients and found no difference between the groups in terms of post-PCI TIMI flow, target vessel revascularization (TVR), in hospital mortality and stent thrombosis (11).

Wang *et al*., compared the intracoronary bolus versus intravenous eptifibatide and concluded that intracoronary regimen reduced mortality, TVR, and 30 days major adverse cardiovascular events (MACE). The bleeding rate was similar among patients in both groups (12).

The literature review showed that in our country, there are limited studies which have been conducted on the comparison of the intracoronary and intravenous administration of Eptifibatide during PCI in patients with ACS; therefore, this study was performed with the aim to compare the effects of intravenous versus intracoronary Eptifibatide on the TIMI frame count during PCI in ACS patients.

Materials and Methods

This non-randomized clinical trial study was performed on 103 patients with acute coronary syndromes who referred to the cardiac emergency ward of Ghaem hospital, Mashhad University of Medical Sciences, and were candidates for urgent coronary angiography and PCI according to the latest ACC / AHA Guidelines in 2011 and 2013. Sampling was done as a non-probable and purpose-based method.

The two-mean comparison formula was used to determine the sample size (based on Deibele's study (10). In this calculation, the first and second type errors were considered as 5% and 10%, respectively. 40 cases were calculated in each group, as follows:

-Numeric Results for Two-Sample T-Test

-Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1≠Mean2

-The standard deviations were assumed unknown and unequal.

-Allocation

-Power N1 N2 Ratio Alpha Beta Mean1 Mean2 S1 S2

-0.90332 39 39 1.000 0.05000 0.09668 20.0 25.0 5.0 8.0

Considering the sample loss during the study period, the sample size increased to 55 patients in each group. During the study, seven patients from the intracoronary administration group were excluded due to incomplete information.

Inclusion criteria were the ACS patients who (according to the latest ACC/AHA Guideline in 2011 and 2013) had an indication of coronary artery angiography and had 75% or more stenosis in at least one epicardial coronary artery and were suitable for PCI and stent insertion.

Exclusion criteria included the patients who had no desire to participate in this research at any stage of the study, pregnancy, severe calcification of coronary arteries, severe stenosis (≥50%) in the unprotected left main coronary artery, contraindication for the use of IIb/IIIa glycoprotein inhibitors, stroke in the last three months, PT>1.5, platelet <100,000/ml, creatinine>4 gr/dl, Hematocrit <30%, history of bleeding disorders, history of allergy to this group of medications.

The protocol was approved by the ethics committee of Mashhad University of Medical Sciences. All cases were asked to sign an informed consent before participation in the study.

Before the entrance to the angiography room, a history was obtained from all patients, which included: age, the risk factors for coronary artery disease such as smoking, history of hypertension, dyslipidemia, and history of diabetes. Coronary angiography was performed in these patients via the right femoral artery

The complications were evaluated only during the patients' hospitalization. Before and 12 hours after PCI, CKMB and standard electrocardiography were performed. Doppler echocardiography was performed in all patients, and LVEF was calculated according to the latest ACC/AHA guidelines. Blood glucose, urea, creatinine, serum lipids, CBC, platelet counts, Hb, HCT, PT, and PTT, were measured in all patients before coronary angiography.

If the patients had not used aspirin and clopidogrel before, they received 300 mg of chewing aspirin and 600 mg of clopidogrel orally at admission. In all patients, immediately prior to PCI, Unfractionated Heparin with a dose of 50 to 70 U/kg was intravenously administered. In these patients, the stent was inserted during PCI. Aspirin, with an unlimited daily dose of 80 mg and clopidogrel with a daily dose of 75 mg, was prescribed for one year. The use of other drugs in ACS patients (such as statins, beta-blockers, nitrates, calcium antagonists, ACEIs, or ARBs) was similar in the two groups. Eptifibatide was administered based on the presence of thrombus, Haziness, and Low TIMI Flow grade at the target coronary artery in coronary angiography (thrombus grade 3 or more).

After conducting the angiography and passage of the wire and before the PCI, the patients were divided into two groups; one group received two doses of Eptifibatide as an intravenous bolus (180 µg/kg with 10 minutes interval), and the other group received the same dose with the same interval but as an intracoronary bolus. Intracoronary injection of this drug was used by a guiding catheter. Then, the infusion continued as 2 µg/min for 12 to 24 hours in patients of both groups. Thrombosuction was performed in patients with STEMI if needed. Bolus intracoronary and intravenous injection of Eptifibetide was performed within 1-2 minutes.

After PCI, the angiography CD from PCI was provided. Patients were evaluated for bleeding and its severity, renal insufficiency, MI, CVA, mortality, and need for CABG during hospitalization. Coronary blood flow was calculated using TIMI Frame Count and Corrected TIMI Frame Count (by an interventional cardiologist who was blind about the route of Eptifibatide administration in each patient). TFC was calculated by observing angiography CD and counting the number of angiographic frames which was performed from the onset of the appearance of the contrast agent at the onset of the coronary artery to the end of the artery. The end of the artery in the RCA (Right Coronary Artery) was considered the first branch separated from the PLV (Posterolateral Vessel), in the LCX (Left Circumflex Artery), the last OM (Obtus Marginal Artery) separated from LCX (Left Circumflex Artery), and in LAD (Left Anterior Descending Artery), the last part of the Bifurcation at the tip of the heart. In order to determine the CTFC, the calculated TFC in the LAD was divided by 1.7 because of the longer length of this artery (13).

Data analysis

Data that were collected from observations of patients' demographic and clinical characteristics were analyzed by SPSS software (version 22) and were described using the appropriate center and dispersion indices. To compare the quantitative variables in the two groups, according to the distribution of variables, the *t*-test was used if it was normal or the Mann-Whitney test was used if it was not normal. A *Chi*-square test was also used to compare qualitative variables into two groups. $P<0.05$ was considered statistically significant.

Results

A total of 103 patients with a mean age of 56.8±11.3 years at a range of 28 to 85 years were studied. Forty-eight patients were treated with an intracoronary injection of Eptifibatide, and 55 received an intravenous injection of Eptifibatide. In the intracoronary injection group, 37 (77.1%) were male, and 11 (22.9%) female, and in the intravenous injection group, 39 (70.9%) were male and 16 (22.1%) female. There was no significant difference between intracoronary and intravenous injection groups in terms of gender distribution ($P=0.477$).

The mean age of patients in the intracoronary injection group was 56.2±13.1 years, and in the intravenous injection group was 57.4±9.7 years. The student t-test showed that mean age was not significantly different between intracoronary and intravenous injection groups ($P=0.601$).

The frequency of diabetes in the intracoronary injection group was 25 (52.1'%), and in the intravenous

injection group was 24 (43.6%). Based on the *Chi*-square test, there was no significant difference between intracoronary and intravenous injection groups in the incidence of diabetes (*P*=0.392).

The frequency of high blood pressure in the intracoronary injection group was 23 (47.9%), and in the intravenous injection group was 19 (34.5%). Chi-square test showed no significant difference between the two groups in the incidence of high blood pressure (*P*=0.168).

The frequency of hyperlipidemia in the intracoronary injection group was 38 (79.2%), and in the intravenous injection group was 48 (87.3%). Chi-square test showed no significant difference between intracoronary and intravenous injection groups in the incidence of hyperlipidemia (*P*=0.269).

The frequency of smoking in the intracoronary injection group was 8 (16.7%), and in the intravenous injection group was 11 (20%). Chi-square test showed that there was no significant difference between intracoronary and intravenous injection groups in the frequency of smoking (*P*=0.663).

In terms of the frequency of acute coronary syndromes, in the intracoronary injection group, there was STEMI in 11 cases (22.9%), NSTEMI in 5 (10.4%), and unstable angina in 32 (66.7%); and in the intravenous injection group, there was STEMI in 17 cases (30.9%), NSTEMI in 9 (16.4%), and unstable angina in 29 (52.7%). Chi-square test showed that the frequency of acute coronary syndromes was not significantly different between the two groups (*P*=0.348).

In terms of the frequency of involved branch in the two groups, in the intracoronary injection group, LAD was in 25 cases (52.1%), LCX in 9 (18.8%), OM in no case, RCA in 14 (29.2%); and in the intravenous injection group, LAD in 32 cases (58.2%), LCX in 5 (9.1%), OM in 2 (3.6%), and RCA in 16 (29.1%). Fischer's exact test showed no significant difference between intracoronary and intravenous injection groups in the frequency distribution of the involved branch (*P*=0.338).

The mean of coronary artery lesion length in the intracoronary injection group was 24.4±10 mm, and in the intravenous injection group was 22.2±10.2 mm; the difference was not statistically significant (*P*=0.224).

The mean of coronary diameter in the intracoronary injection group was 2.9±0.3 mm, and in the intravenous injection group was 2.8±0.2 mm; the difference was not statistically significant (*P*=238).

The mean coronary artery stenosis severity in the intracoronary injection group was %96.4±5.3, and in the intravenous injection group was %96.3±5.3; this difference was not statistically significant (*P*=0.920).

The frequency of coronary artery thrombosis in the intracoronary injection group was 34 (70.8%), and in the intravenous injection group was 31 (57.4%); no significant difference was observed between two groups (*P*=0.159).

The frequency of thrombectomy in the intracoronary injection group was 9 (18.8%), and in the intravenous injection group was 8 (14.8%), which did not show significantly different between two groups (*P*=595).

The mean serum CKMB level in the intracoronary injection group was 64.7±71.2 mg/dl, and in the intravenous injection group was 86.0±100.6 mg/dl; this difference was not significantly different between two groups (*P*=0.204).

The mean LVEF in the intracoronary injection group was 44.9±11.5, and in the intravenous injection group was 43.6±11.2, and this difference was not significantly different (*P*=0.587).

The mean TIMI frame count in the intracoronary injection group was 11.9±4.35, and in the intravenous injection group was 11.9±4.8, and this difference was not significantly different (*P*=0.980).

The mean TIMI Frame Count of patients with STEMI in intravenous injection group was

11.7±5.5 and 11.3±3.1 in the intracoronary injections, and this difference were not statistically significant (*P*=0.778).

The mean TIMI Frame Count of NSTEMI patients in the intracoronary injection group was 12.7±2.1, and in the intravenous injection group was 11.3±3.2, and this difference was not significant (*P*=0.420).

The mean TIMI Frame Count of unstable angina patients in the intracoronary injection group was 11.8±4.2, and in the intravenous injection group was 12.4±5.2, and this difference was not statistically significant (*P*=0.603).

The complications were observed in 11 patients (22.9%) of the intracoronary injection group and 9 (16.4%) of the intravenous injection group; the difference was not significant (*P*=402).

The mean of TIMI Frame Count in the intracoronary injection group with LAD involvement was 10.5±3.8, LCX involvement 12.2±4.4, and RCA involvement 14.2±4.6, and 14.24±6.4 in the intravenous injection group with LAD involvement was 11.1±3.0, LCX involvement was 10.8±4.4 and RCA involvement was 14.1±5.9. Based on Student's t-test, there was no significant difference between mean TIMI Frame Count

of patients with different coronary arteries in the intracoronary and intravenous injection groups (In LAD, *P*=0.518; For LCX, *P*=0.576; and in RCA, *P*=0.964).

In the intracoronary injection group, minor bleeding, major bleeding, and MI were observed in 4 (8.3%), 2 (4.2%), and 5 (10.4%), respectively and in the Intravenous injection group were observed in 3 (5.4%), 0, and 6 (10.9%), respectively. The frequency of the types of complications was not significantly different between the two groups of intracoronary and intravenous injection (*P*= 0.358).

Eleven patients (10.7%) had myocardial infarction after treatment, of which 5 (10.4%) were in the intracoronary injection group and 6 (10.9%) in the intravenous injection group. The frequency of myocardial infarction was not significantly different between the two groups (*P*=0.936).

A summary of the results is displayed in Table 1.

Table 1. Demographic characteristic of patients

Variables	Intravenous	Intracoronary	*P*
Age (years)	57.4 ± 9.7	56.2 ± 13.1	0.601
Gender (Male)	39 (70.9)	37 (77.1)	0.477
Hypertension	19 (34.5)	23 (47.9)	0.168
Diabetes	24 (43.6)	25 (52.1)	0.392
Smoking	11 (20)	8 (16.7)	0.663
Dyslipidemia	48 (87.3)	38 (79.2)	0.269

Table 2:characteristrics of ACS, coronary artery involvement, CKMB level and LVEF in two groups

Variables		Intravenous	Intracoronary	*P*
ACS	**STEMI**	17 (30.9)	11 (22.9)	0.348
	NSTEMI	9 (16.4)	5 (10.5)	
	unstable angina	29 (52.7)	32 (66.7)	
Involved coronary branch	**LAD**	32 (58.2)	25 (52.1)	0.338
	LCX	5 (9.1)	9 (18.8)	
	RCA	16 (29.1)	14 (29.2)	
	Lesion length	22.0 ±10.5	24.4 ± 10.8	0.244
	Involved coronary diameter	2.8±0.2	2.9±0.3	0.238
	Involved coronary stenosis	96.3±5.3	96.4±5.3	0.920
	Involved coronary thrombus	31 (57.4)	34 (70.8)	0.159
	thrombectomy	8 (14.8)	9 (18.8)	0.595
	CKMB	86.0 ± 100.6	64.7 ± 71.2	0.204
	LVEF	43.6±11.2	44.9 ± 11.5	0.204

Table 3. TIMI Frame Count and complications in two groups

Variables		Intravenous	Intracoronary	*P*
TIMI Frame Count	**STEMI**	11.3±3.1	11.7±5.5	0.778
	NSTEMI	11.3±3.2	12.7±2.1	0.420
	unstable angina	12.4±5.2	11.8±4.2	0.603
	LAD	11.1 ± 3.0	10.5 ± 3.8	0.518
	LCX	10.8 ± 4.4	12.2 ± 4.4	0.576
	RCA	14.1 ± 5.9	14.2 ± 4.6	0.964
	In total patients	11.9±4.38	11.9±4.35	0.980
	MACE	9 (16.3)	11 (22.9)	0.402
	Minor bleeding	3 (5.4)	4 (8.3)	0.358
	Major bleeding	0	2 (4.2)	
	MI	6 (10.9)	5 (10.4)	

Discussion

According to the results of this study, there was no significant difference between intracoronary and intravenous injection of Eptifibatide regarding age, gender, risk factors for coronary artery atherosclerosis. Also, the mean of serum CKMB level, length of the lesion, diameter, and stenosis severity of coronary

arteries, frequency of thrombus, thrombectomy, and LVEF was not significantly different in two groups. Moreover, there was no significant difference between the two groups in the incidence of complications such as bleeding (minor and major), MI, CVA, and death during hospitalization and after PCI. Also, after PCI and drug injection, the velocity of arterial blood flow in the coronary artery was calculated using the TFC method; this parameter was not significantly different in two methods of intravenous and intracoronary injection of Eptifibatide. It was also compared in patients with STEMI, NSTEMI, and UA in two groups, separately, which did not show significant differences.

The studies which have been done recently compared the effects of two methods of injection of this drug in patients during PCI, all of them have been performed on limited sample size (11,14), and done in patients with STEMI; fewer studies have evaluated the patients with NSTE ACS; the variable results were reported.

Pinto *et al*., in their small study, evaluated the role of intracoronary injection of eptifibatide in primary PCI for the first time. No major bleeding was reported, and minor bleeding occurred only in two cases; no adverse effects (especially arrhythmia) were noted during the intracoronary administration. In these patients, there was no emergency cardiac surgery, myocardial re-infarction, and no cases of death were reported (15). In our study, the complications were found in 11 patients in intracoronary injection and 9 cases in the intravenous injection of Eptifibatide; the difference was not statistically significant (P=0. 402). Complications in our study were more than the study of Pinto and 11 patients had myocardial infarction after treatment; this difference can be due to the difference in the severity of heart disease and the presence of underlying factors and also the type of acute coronary syndrome. In the study by Pinto *et al*., it was found that normal myocardial perfusion occurs in a large number of patients with the intracoronary injection of eptifibatide. In our study, there was no significant difference between the effects of two methods of injection, and both methods were effective and safe.

In the study by Esfandi and colleagues at Qazvin University of Medical Sciences in 2016, 76 patients with STEMI during Primary PCI were compared in terms of intracoronary and intravenous eptifibatide injection; they concluded that intracoronary injection group had better myocardial reperfusion and had better clinical prognosis in follow-up (15). In our study, there was no significant difference between the effects of two methods of injection. This difference may be due to the difference in the number of patients; the number of patients in our study was 103, and in Esfandi's study was 76. Also, the mean age of STEMI patients in our study was 60 years, which was slightly higher than that of Esfandi's study.

In a study conducted by Safi and colleagues in 2012, 40 patients with STEMI were compared in terms of the effect of intracoronary and intravenous administration of Eptifibatide; they concluded that no difference was found in the incidence of increasing cardiac markers, TIMI Grade 3 Flow, MI extension, bleeding, emergent revascularization, recurrent infarction, and mortality rate. Although it was found that intracoronary administration of the drug is safe, it is not superior to intravenous administration (16). Their results were consistent with the findings of our study.

A meta-analysis that was published by Friedland *et al*., compared the effects of intracoronary versus intravenous administration of IIb-IIIa inhibitors in percutaneous coronary interventions for the acute coronary syndrome. Ten randomized controlled trials were included in the analysis. Intracoronary use of the drugs was associated with a significantly lower short-term mortality and short-term target vessel revascularization (TVR) with the same bleeding rates. In this meta-analysis, the prevalence of TIMI grade 3 flow was greater in the intracoronary injection group (17).

Sanati *et al*., which compared intracoronary versus intravenous eptifibatide during percutaneous coronary intervention for acute ST-segment elevation myocardial infarction, concluded that by modifying the route of administration of eptifibatide, the clinical effect might be preserved without increasing the short-term mortality and procedural failure (18). Also, Namazi and colleagues compared the efficacy of intracoronary Abciximab vs. intravenous Eptifibatide in primary PCI; they reported that the intracoronary administration of Abciximab was not superior to the intravenous administration of Eptifibatide in the STEMI patients who underwent primary PCI (19).

However, in recent years, some randomized trials have demonstrated that glycoprotein inhibitors administered as intracoronary are safe and effective in reducing the infarct size and providing better clinical outcomes than when given intravenously, without a significant increase in major bleeding (15,20). Furthermore, no adverse events were reported during the intracoronary administration of glycoprotein inhibitors, compared with the IV route, which is associated with any significant delay in revascularization (15). Moreover, other studies reported that to optimize the

drugs' action and to maximize the antiplatelet properties while reducing the undesired side effects, early initiation, bolus only, intracoronary injection, and use of perfusion catheters are suggested methods to achieve the goals mentioned (21-23).

The most important limitation of the present study was the low number of patients, which led to different results. In order to achieve more precise results and to determine the superiority of one of these two approaches to another, further studies with more sample sizes should be performed. In addition, it is also necessary to assess the results and effects of these measures in the long term.

The effects and complications of Eptifibatide were not significantly different in Intracoronary and intravenous administration in ACS patients during PCI and at the time of patients' hospitalization.

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