Impact of Maintenance Dose of Eptifibatide in Patients with ST-Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Coronary Intervention

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Abstract

Aim: ST-segment elevation myocardial infarction (STEMI) is usually caused by a rupture in the atherosclerotic plaque, followed by platelet aggregation which ultimately leads to acute coronary artery occlusion. In this study, we investigated the effect of maintenance dose of Eptifibatide (intravenous drug of GP IIb/IIIa inhibitor) in patients with STEMI who underwent primary percutaneous coronary intervention (PPCI). Methods: 264 patients who had acute chest pain suggestive of STEMI were entered in the study. All patients received the same dose of bolus dose of eptifibatide. Then the patients were randomly divided into two groups, one group (n=147) received a maintenance dose of intravenous eptifibatide (infusion of 2?g/kg/min) and the other group (n=117) did not receive this treatment. All patients were evaluated 1 and 3 months after the start of treatment in terms of predicted outcomes. Results: The occurrence of three-month MACE between the case and control groups did not have a statistically significant difference (28.6% versus 35.0% ; P-value: 0.286). Re-hospitalization occurred in 10 patients (6.8%) from the case group and 30 patients (25.6%) from the control group, which was statistically significant (P-value: 0.000). Also, investigations showed that the rate of re-infarction (P-value: 0.024) and target lesion revascularization (P-value: 0.003) was significantly lower in the group that received Eptifibatide infusion. Conclusion: Eptifibatide maintenance dose infusion in patients who undergo PPCI in the context of STEMI, does not significantly reduce MACE, although it does significantly reduce re-hospitalization and re-infarction. It also does not increase the risk of bleeding and cerebrovascular events.

Introduction

Coronary artery disease is a widespread cardiac disease that occurs by plaque formation on coronary artery wall. Coronary artery disease is the first and most important death reason in today's societies. In addition, this disease leads to disability and high morbidity. What conventionally was called a heart attack, is more precisely called acute coronary syndrome nowadays. Patients who go to the emergency room with acute coronary syndromes (ACS) will divided into Two groups include ST-segment elevation myocardial infarction (STEMI) and coronary syndromes without ST-segment elevation (NSTE ACS) (1,2).

Despite the decrease in mortality rate due to STEMI in recent years, this disease still remains a common clinical and challenging condition with high mortality risk. Each year, approximately 258,000 patients in the United States present to the emergency department with a diagnosis of STEMI, with an incidence of 7.3 per 10,000 (3).

STEMI is usually caused by a rupture or erosion in the atherosclerotic plaque, followed by platelet aggregation and thrombosis which ultimately leads to acute coronary artery occlusion and myocardial damage and

therefore requires emergency treatment. The preferred treatment strategy includes emergency reperfusion through primary percutaneous coronary intervention (PPCI). Reperfusion of coronary blood flow as soon as possible after acute ST-segment elevation myocardial infarction improves disease outcomes (4).

Of course, despite reperfusion of blood flow in the coronary arteries that caused the infarct, there is myocardial perfusion disorder in some patients who have undergone successful PCI, which is associated with a larger infarct size and an increase in long-term cardiac mortality (4,5). One of the main causes of myocardial reperfusion disorder is the embolization of thrombotic substances including platelet aggregations in the distal microcirculation. Widespread use of PCI may also create a thrombotic condition due to wounding the vessel wall and stimulate platelet activation and proliferation of new intima (6).

The first step to initiate arterial thrombosis is endothelial damage and exposure of subendothelial matrix glycoprotein (GP) to circulating platelets, followed by platelet adhesion (7). GP IIb/IIIa are the most abundant integrins on the surface of platelets, which turn into a ligand-accepting form after the activation of platelets. Ligands such as fibrinogen bind to GP IIb/IIIa of adjacent platelets and lead to platelet aggregation and thrombus formation. (8)

In recent years, the implementation of adjunctive mechanical and pharmacological therapies during PPCI has significantly improved clinical outcomes in STEMI patients. Among these treatments, aspirin and P2Y12 inhibitors can be mentioned, which play an essential role in the medical treatment of STEMI patients (9, 10).

Among other treatments, thrombus aspiration and the use of GP IIb/IIIa inhibitors can be mentioned, which have significantly reduced the incidence of distal embolization and improved reperfusion of capillary blood flow and clinical outcomes in STEMI patients. However, this approach may also have disadvantages, meaning that any effective antiplatelet regimen may be associated with an increased risk of bleeding, and often discontinuation of long-term therapy potentially worsens outcomes (11-14).

Three intravenous drugs of GP IIb/IIIa inhibitors namely Abciximab, Eptifibatide and Tirofiban are widely used in PCI and in the treatment of ACS. Eptifibatide is a peptide containing the amino acid sequence of arginine, glycine and aspartate with a half-life of 2.7 hours, which binds to GP IIb/IIIa receptors and prevents the binding of fibrinogen to receptor and causes an anti-platelet effect. On the other hand, inhibition of GP IIb/IIIa reduces the activation of prothrombin replication factors. Therefore, inhibition of GP IIb/IIIa may have both antiplatelet and anticoagulant effects (7,8,15,16). The dose used in the treatment of STEMI is intravenous bolus dose of 180μg/kg and infusion of 2μg/kg/min for a maximum time of 18 hours (9).

According to European and American guidelines, intravenous injection of GP IIb/IIIa inhibitors in patients with STEMI who underwent PPCI and have evidence of high thrombosis or no-reflow phenomenon seems reasonable (Class: IIa, LoE: C) (9,10). However, so far few studies (Low Level of Evidence) have investigated the effect of maintenance dose of Eptifibatide in STEMI patients who underwent PPCI. Therefore, in this study, we investigated the effect of maintenance dose of Eptifibatide in patients with STEMI who underwent PPCI.

Methods

Patient Selection

The study population is patients older than 18 years old who visited Fatemeh Zahra Sari Heart Hospital, located in the north of Iran, between September 2017 and August 2018 and underwent PPCI with STEMI. The people in the study included patients who had chest pain suggestive of myocardial infarction from at least 30 minutes before admission to a maximum of 12 hours before going to the hospital with an ECG suggestive of STEMI.

Patients who presented with cardiogenic shock, patients who became candidates for PCI after receiving fibrinolytics, patients who became candidates for emergent CABGs after angiography, patients under 18 years old or over 80 years old, pregnant patients, patients with kidney or liver failure and Patients who had

contraindications for eptifibatide use (active internal bleeding, brain neoplasm or aneurysm, stroke in the last two years, intracerebral trauma or surgery in the last two months, uncontrolled high blood pressure, and thrombocytopenia) were excluded from the study.

Study Design and Ethics

This study was a prospective, double-blind, randomized controlled clinical trial that was conducted on 264 patients with STEMI who underwent PPCI. The sample size of this study was (calculated based on statistical formulas and after 10% downfall), 264 people. All these patients were treated similarly with aspirin (300 mg), clopidogrel (600 mg) and statin after electrocardiographic confirmation of STEMI. Then all patients underwent PPCI. Regarding the angiography method, femoral approach was preferred. All patients received the same dose of intravenous heparin and bolus dose of eptifibatide (180 µg/kg/10 min). Then the patients were randomly divided into two groups, one group (n=147) received a maintenance dose of intravenous eptifibatide (infusion of 2µg/kg/min) and the other group (n=117) did not receive this treatment. Randomization was done by sealed envelopes at the end of the procedure. Administering the maintenance dose of eptifibatide started during the first hour after the bolus dose injection and continued for 12 hours. Standard medical treatment of ACS after PCI was performed based on guidelines and the same in both groups with aspirin (80 mg), clopidogrel (75 mg), lipid-lowering drugs, beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin receptor blockers (ARBs). (9, 10). All patients were re-evaluated 1 and 3 months after the start of treatment in terms of predicted outcomes.

Also, the objectives of this research project and its implementation method were explained to all patients, and they entered this project after obtaining oral and written informed consent. It should be noted that this study was registered and approved by the Ethics Committee of Mazandaran University of Medical Sciences before its implementation.

Primary and Secondary Outcomes

The primary outcomes in this study were re-hospitalization and major adverse cardiovascular events (MACE), a composite of cardiovascular death, reinfarction, cerebrovascular events, major bleeding, target vessel revascularization (TVR), and target lesion revascularization (TLR).

Major bleeding based on the standardized definitions of bleeding for cardiovascular clinical trials includes: fatal bleeding that leads to death within 7 days, intracranial or retroperitoneal bleeding, bleeding that is accompanied by a drop of at least 3-5 units of hemoglobin or need to inject at least 2-4 units of blood, bleedings that lead to hemodynamic disorders and require intervention, access site bleedings that require intervention, and hematoma with a size of 5 cm or more (17).

TVR was defined as unplanned repeat PCI or bypass graft placement for a stenosis in another part of the vessel treated at the index PCI (ie, exclusive of TLR events). TLR was defined as repeat PCI or bypass graft placement for restenosis at the lesion treated during index PCI or occurring within 5 mm of the PCI site (18).

Secondary outcomes include separate examination of in-hospital and out-of-hospital death due to cardiovascular diseases, re-infarction, cerebrovascular events, major bleeding, minor bleeding, TVR and TLR.

Statistical Analysis

The obtained data were entered into SPSS software (Statistical Package for the Social Sciences) version 24. First, they were summarized using methods based on descriptive statistics, including the mean ± standard deviation for quantitative variables (such as age) and frequency tables for qualitative variables, and then to compare the groups in terms of background variables, using the t-test, Chi-square and finally logistic regression were analyzed. P-value less than 0.05 was considered significant.

Results

Study Population

Demographic and clinical characteristics of all patients are shown in Table 1. There was no significant difference between the two groups in terms of gender and age. Among the patients participating in the study, 147 people were in the intervention group, 95 of them were men (64.6%) and 52 were women (35.4%), and their average age was 59.85. Also, out of 117 patients participating in the control group, 65 were men (55.6%) and 52 were women (44.4%), whose average age was 61.78. In terms of coronary artery disease risk factors (diabetes mellitus, hypertension, hyperlipidemia and cigarette smoking) there was no significant difference between the two groups.

Also, out of the total of 147 patients studied in the intervention group, the location of myocardial infarction in 56.5% of cases was in the anterior regions, 39.3% in the lower regions and in 4.6% in the lateral regions. In the control group, the location of myocardial infarction in 45.3% of cases was in the anterior regions, in 52.1% in the lower regions and in 2.6% in the lateral regions, and also in this sense, no significant difference was observed between the two studied groups (Table 2).

Primary Outcomes

The studied patients were followed up for three months after PPCI in terms of re-hospitalization (Figure 1). Re-hospitalization occurred in 10 patients (6.8%) from the case group and 30 patients (25.6%) from the control group, which was statistically significant (P-value: 0.000).

Considering the low mortality rate in STEMI patients who undergo PPCI, in order to investigate the effect of Eptifibatide drug on the consequences and cardiovascular complications, the patients participating in this study in terms of MACE, which includes a combination of death due to cardiovascular diseases, Re-hospitalization, re-infarction, cerebrovascular events, major bleeding, target vessel revascularization (TVR) and target lesion revascularization (TLR) were divided into two groups (Figure 2): The group that experienced MACE and the group that did not experience MACE. The results of our study showed that the occurrence of three-month MACE between the case and control groups did not have a statistically significant difference (42 patients equivalent to 28.6% in the case group versus 41 patients equivalent to 35% in the control group), which means that receiving a maintenance dose of Eptifibatide did not significantly reduce the combination of mortality and morbidity in the patients (P-value: 0.286).

Also, the three-month MACE rate in the case and control groups was compared in different subgroups (Table 3). These findings showed that in our studied patients, the relationship between the occurrence or non-occurrence of MACE after Eptifibatide infusion with hypertension and hyperlipidemia is significant. This means that in patients with hypertension and hyperlipidemia, Eptifibatide infusion has significantly reduced mortality and morbidity. Of course, this relationship was not seen in diabetic patients and smokers.

Secondary Outcomes

Three months after PPCI, secondary outcomes including in-hospital and out-of-hospital death due to cardiovascular diseases, re-infarction, cerebrovascular events, major bleeding, minor bleeding, TVR and TLR were investigated (Table 4). Investigations showed that the rate of re-infarction and performing TLR was significantly lower in the group that received Eptifibatide infusion, while there was no significant difference of death due to cardiovascular diseases, cerebrovascular events, major and minor bleeding and TVR between two groups.

Discussion

Our study showed that in STEMI patients who underwent PPCI, although Eptifibatide maintenance dose infusion, causes a significant reduction in re-hospitalization, re-infarction and TLR, it does not cause a significant reduction in MACE.

The most studied GP IIb/IIIa inhibitor in patients with STEMI who undergo PPCI is Abciximab (8). Although previous large studies showed that administration of Abciximab in patients undergoing PPCI due to STEMI reduces death, reinfarction and ischemic events (19, 20), subsequent studies showed that its administration especially in patients whom receive thienopyridine drugs at the same time, does not significantly

reduce death and re-infarction (21,22). However, the results of our study showed that the administration of Eptifibatide in a subgroup of patients with hypertension and hyperlipidemia reduces MACE. Whether this effect of the drug is related to the primary antiplatelet effect of Eptifibatide or the non-specific anti-inflammatory properties of it is not determined by our study.

In 2010, Zeymer and colleagues in the EVA-AMI Trial showed that Eptifibatide infusion, as an adjunct to PPCI in the treatment of STEMI, is as effective as Abciximab, and even the rate of re- infarction was significantly lower with Eptifibatide, while There was no significant difference of the bleeding rate between the two groups (23). This finding is consistent with the lower rate of re-infarction in our intervention group.

So far, many studies have been published on the adjuvant effect of Eptifibatide infusion in patients undergoing PCI. One of the most important studies is the ESPRIT Trial. The findings of this study showed that the administration of Eptifibatide leads to a significant reduction of 48-hour and 30-day MACE (combination of death, myocardial infarction and TVR) (24). The inconsistency of the results of our study with ESPRIT Trial can be due to the smaller sample size of our study (264 patients vs. 2064 patients) and also the shorter infusion time of this drug in our study (12 hours vs. 24-18 hours) and as a result receiving a lower dose of the drug. GP IIb/IIIa inhibitors block the binding of circulating fibrinogen and von Willebrand factor to the GP IIb/IIIa receptor thus preventing the cross-linking of platelets necessary for aggregation and thrombosis. These agents have also been shown to disaggregate freshly formed, platelet-rich thrombi in a "dose-dependent manner" ranging from no disaggregation at low doses up to significant disaggregation at clinically relevant doses (25).

Most of the studies conducted on Eptifibatide are on patients who are candidates for PCI in the context of NSTE ACS. To our knowledge, few clinical trials have been conducted on the effect of Eptifibatide in patients undergoing PPCI due to STEMI. Among these clinical trials is a study that was conducted between 2000-2009 in the United States and showed that the administration of Eptifibatide reduces mortality in STEMI patients who undergo PPCI (25), while the study by Le May et al, and the study of Shariati et al, showed that the administration of this drug does not reduce MACE (combined mortality and recurrent myocardial infarction) (13,26). These observations however have not been fully supported by a retrospective analysis of clinical outcomes in the ESPRIT trial, accepting that this was not a primary PCI study and not everyone in the preloading group received the 600mg dose of Clopidogrel, the study demonstrated that the efficacy of Eptifibatide was maintained irrespective of Thienopyridine preloading.

Also, our study showed that Eptifibatide administration does not increase major and minor bleeding and cerebrovascular events. One of the reasons for the low rate of bleeding in the present study is the careful selection of patients based on the inclusion and exclusion criteria, which reduces the chance of bleeding. The homogeneity of the two groups in terms of the amount of major and minor bleeding shows that the possibility of bleeding complications should not prevent the administration of this drug infusion in high-risk patients.

Our study shows that the adjunctive use of Eptifibatide in patients presenting with STEMI and undergoing PPCI treatment does not reduce MACE but reduces re-hospitalization, re-infarction and TLR, and may be associated with improved clinical outcomes, especially as it does not increase the risk of bleeding and cerebrovascular events. In future studies in STEMI patients (an area where the effect of Eptifibatide has not been sufficiently investigated), with a larger sample size and with a higher power, its generalizability to the community and its validity can be improved.

Conclusion

Eptifibatide maintenance dose infusion in patients who undergo PPCI in the context of STEMI, does not significantly reduce MACE, although it does significantly reduce re-hospitalization, re-infarction and TLR. It also does not increase the risk of bleeding and cerebrovascular events**.**

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Table 1. Patients' demographics and clinical characteristics.

P-value	Control group	Case group		
0.163	55.6) 65%)	64.6) 95%)	Male	Sex
	44.4) 52%)	%)35.4) 52	Female	
0.621	50.4) 59%)	79 (53.7%)	Years<60	Age
	49.6) 58%)	68 (46.3%)	Years>60	
0.891	29.1) 34%)	27.9) 41%)	+	Diabetes
	70.9) 83%)	72.1) 106%)	-	
0.163	52 (44.4%)	52 (35.4%)	+	Hypertension
	65 (55.6%)	64.6) 95%)	-	
0.146	37.6) 44%)	28.6) 42%)	+	Hyperlipidemia
	62.4) 73%)	71.4) 105%)	-	
0.120	31 (26.5%)	41 (27.9%)	+	Cigarette smoking
	86 (73.5%)	106 (72.1%)	-	

Table 2. The location of myocardial infarction in case and control groups.

			Amount (percent)	Total	P-value
Location of Myocardial Infarction	Case	Anterior	83 (56.5)	147	0.127
		Inferior	58 (39.3)		
		Lateral	6 (4.1)		
	Control	Anterior	53 (45.3)	117	
		Inferior	61 (52.1)		
		Lateral	3 (2.6)		

Table 3. The three-month MACE rate in different subgroups.

		MACE -	MACE +	P-value
Diabetes	+	53 (29.3%)	22 (26.5%)	0.642

		MACE -	MACE +	P-value
	_	128 (70.7%)	61 (73.5%)	
Hypertension	+	64 (35.3%)	40 (48.2%)	0.042
	_	117 (64.7%)	43 (51.8%)	
Hyperlipidemia	+	48 (26.5%)	38 (45.8%)	0.020
	_	133 (73.5%)	45 (54.2%)	
Cigarette smoking	+	48 (26.5%)	24 (28.9%)	0.685
	_	133 (73.5%)	59 (71.1%)	

Table 4. Secondary outcomes after primary PCI in case and control groups.

P value	Control group	Case group		
1.00	(%1.7) 2	(%1.4) 2	+	In-hospital death due to cardiovascular disease
	(%98.3) 115	(%98.6) 145	_	
0.307	2 (1.7%)	(%4.1) 6	+	Out of hospital death due to cardiovascular disease
	115 (98.3%)	(%95.9) 141	_	
0.307	(%1.7) 2	(%4.1) 6	+	Major bleeding
	(%98.3) 115	(%95.9) 141	_	
0.696	(%1.7) 2	(%2.7) 4	+	Minor bleeding
	(%98.3) 115	(%97.3) 143	_	
0.257	(%0) 0	(%2) 3	+	Cerebrovascular events
	(%100) 117	(%98) 144	_	
0.024	(%6) 7	(%0.7) 1	+	Re-infarction
	(%94) 110	(%99.3) 146	_	
0.003	(%9.4) 11	(%1.4) 2	+	TLR
	(%90.6) 106	(%98.6) 145	_	
0.100	16 (13.7%)	15 (10.2%)	+	TVR
	101 (86.3%)	132 (89.8%)	_	

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