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Comparing efficacy of receiving different dosages of eptifibatide in bleeding after percutaneous coronary intervention in patients with myocardial infarction

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Original Article

Abstract

BACKGROUND: Acute coronary syndrome (ACS) is a common condition that needs appropriate treatment like percutaneous coronary intervention (PCI). Glycoprotein IIb/IIIa inhibitors (GPI) like eptifibatide prevent procedural ischemic complications after PCI. Eptifibatide has increased the risk of bleeding complications, although it is effective in reducing mortality and morbidity. Eptifibatide is routinely used in bolus and infusion forms and the aim of this study is to evaluate the efficacy of bolus-only dose and bolus + infusion strategy for administrating eptifibatide in bleeding complications and consequences after PCI.

METHODS: This randomized clinical trial was conducted on subjects who experienced PCI after incidence of myocardial infarction (MI). Patients were randomly divided into two groups who received bolus-only dose (n = 51) or bolus + infusion form of eptifibatide (n = 50). Then, PCI blood pressure, mean time duration of hemostasis after arterial sheath removal, laboratory data, need for blood transfusion, and presence of bleeding complications were evaluated. After 6 months, patients were followed for needs for additional coronary interventions.

RESULTS: The mean age of participants was 61.68 ± 1.50 years. The prevalence of men was 70.29%. There was no significant difference in mean of systolic blood pressure (SBP) and diastolic blood pressure (DBP) during hospitalization ($P > 0.050$). The mean time duration of hemostasis was 8.13 ± 0.45 minutes in the bolus-only group and 16.46 ± 0.71 minutes in the bolus + infusion group ($P < 0.001$). There was no significant difference in the hemoglobin (Hb) level, platelet count, white blood cell (WBC), blood urea nitrogen (BUN), and creatinine level ($P > 0.050$).

CONCLUSION: The results of this study suggested that bolus-only dose of eptifibatide before PCI could be able to decrease significantly bleeding complication and other clinical and cardiovascular outcomes.

Keywords: Eptifibatide, Percutaneous Coronary Intervention, Bleeding, Dosage, Infusion, Myocardial Infarction

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Introduction

About 17 million people worldwide die due to cardiovascular diseases (CVDs) including acute coronary syndrome (ACS).[1] ACS is a common condition caused by plaque rupture and thrombosis which needs proper treatment interventions.[2]

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The main aim of treatment is establishing reperfusion which is done by fibrinolytic therapy or percutaneous coronary intervention (PCI).[3]

Glycoprotein IIb/IIIa inhibitors (GPI) are potent antagonists for platelet aggregation that can prevent procedural ischemic complications after PCI.[4] GPI have anti platelet, anti-thrombotic, and anti-inflammatory features and studies reported that treating patients with ACS with GPI before PCI can improve this intervention efficacy and facilitate it.[5,6]

Eptifibatide (Integrilin®, Millennium, Schering-Plough Corporation) is a GPI that inhibits adhesion of fibrinogen and von willebrand factor (VWF) to GP IIb/IIIa receptors and usually is prescribed in combination with aspirin or heparin in patients with angina who are candidate for coronary interventions.[7] In patients with myocardial infarction (MI) who were treated with PCI, using high dose of eptifibatide reduced 35% of mortality and morbidities.[8] Recent studies reported that routine treatment with eptifibatide had significant clinical benefits and reduced death rate, MI, and need for urgent revascularization.[9]

Although administrating eptifibatide in patients who are candidate for PCI is beneficial, this type of medication increases risk of bleeding, which leads to discontinuing treatment with this medication.[8] Extended eptifibatide infusion after successful PCI has a number of complications. Long-term exposure to this medication can increase the risk of bleeding after arterial sheath removal. In addition, extended infusion of medications increases hospital stay of patients who underwent PCI and rises practical issues related to post-PCI inter-hospital transport.[10] In a cohort study on patients with MI who experienced PCI using one bolus dose of eptifibatide in comparison to routine treatment, no significant differences in clinical outcomes and complications were observed, but one bolus dose of eptifibatide was more cost-effective.[11] According to the wide use of GPI medications like eptifibatide in patients who are candidate for PCI and the high prevalence of bleeding complications of these medications, evaluating suitable treatment time duration of them is necessary. This study aimed to compare the effect of receiving bolus-only dose and bolus + infusion form of eptifibatide on bleeding complications and consequences after PCI on patients with MI in Isfahan, the third populated province in Iran.

Materials and Methods

Study design and population: This nonrandomized clinical trial was done from February 2015 to September 2016 in the Chamran Hospital which is a referral university hospital in Isfahan. The study design was approved by regional bioethics research committee of Isfahan University of Medical Science (IRCT code: IRCT2017071935183N1).

In total, 108 patients who suffered from MI and were candidate for angioplasty interventions entered in the study and after obtaining written content and considering exclusion criteria, 101 subjects were analyzed. The inclusion criteria were: 1) age more than 18 years, 2) increased troponin enzyme level, 3) electrocardiogram (ECG) changes, 4) being candidate for angioplasty, 5) having no contraindication for administrating eptifibatide, and 6) patient's willingness to participate in this study. Exclusion criteria included: 1) history of stroke, 2) treating with anti-coagulants, 3) treating with medications that had interaction with eptifibatide, 4) being candidate for angiography without PCI, 5) being candidate for thrombectomy, 6) sensitivity to eptifibatide, 7) having uncontrolled high blood pressure, 8) dialysis patients, and 9) patient's unwillingness to participate in this study. In addition, the patient's creatinine clearance < 50 mg/min was another exclusion criterion. About 1 mcg/kg/min of eptifibatide was infused and if patients had creatinine > 4 mg/dl, they were excluded from study. All patients were monitored in hospital after PCI.

Procedure and variables assessment: Sample size was determined based on the previous studies. Patients were selected by using availability sampling methods and then divided into two groups using random sampling allocation system. Patients in both groups received 180 mcg/kg eptifibatide in bolus form from peripheral vessel in 8 minutes during their PCI. After PCI, patients in the first group received routine treatment including 75 mg Clopidogrel in every 12 hours. Patients in the second group received routine treatment in addition to 10-hour infusion of 2 mcg/kg/min eptifibatide with maximum dose of 15 mcg/hour.

After that intervention data were extracted from each patient's records, they were entered in the questionnaire as follows: demographic data (age and gender), physical examination outcomes [mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) during hospitalization and the lowest SBP and DBP, the mean time duration of hemostasis after sheath removal], laboratory data during hospitalization and discharge [hemoglobin (Hb), platelet, white blood cell (WBC), blood urea nitrogen (BUN), creatinine], need for receiving blood

products, and presence of bleeding and hematomas during hospitalization. After discharge of patients, they were followed for 6 months and after 6 months, authors contacted patients with telephone call and asked them if they had experienced any cardiovascular intervention during these 6 months.

Statistical analysis: Data were entered into SPSS software (version 19, SPSS Inc., Chicago, IL, USA) and then analyzed. For reporting quantitative and qualitative variables, we used mean ± standard deviation (SD) and number and percentage, respectively. Kolmogorov–Smirnov test (K-S test) was used for checking normality assumption. For analyzing quantitative variables, t-test was used and for comparing qualitative variables chi-square test (or Fisher's exact test) was used. P-value less than 0.050 was consider as statistically significant.

Results

In this study, 120 patients were assessed for eligibility and 12 of them were excluded because of not meeting inclusion criteria (n = 5) or declining to participate in this study (n = 7), and 108 patients were randomly divided into two groups, each group containing 54 patients. Figure 1 shows that how 101 patients (51 in the first group and 50 in the second group) were analyzed. In this study, the mean age of participants was 61.68 ± 1.50 years. Among participants, 20.80% (n = 21), 27.72% (n = 28), and 51.48% (n = 52) had ST-elevation MI (STEMI), Non-STEMI, and stable ischemic heart diseases (SIHds), respectively. There were not any significant differences between two groups in distribution of these types of CVDs (P = 0.710).

In the first 96 hours after PCI, patients did not show any deaths, MI, or stroke in both groups. The need for receiving blood products in the first week after PCI was occurred in 5.8% (n = 3) of patients in the first group and no patients in the second group needed this blood transfusion (P = 0.310).

The mean time duration of hemostasis after sheath removal was 8.13 ± 0.45 minutes and 16.46 ± 0.71 minutes in the first and second groups, respectively (P < 0.001). The mean SBP and DBP and also the lowest SBP and DBP during hospitalization were not statistically different between two groups (P = 0.320 and P = 0.630 for SBP, P = 0.510 and P = 0.400 for DBP).

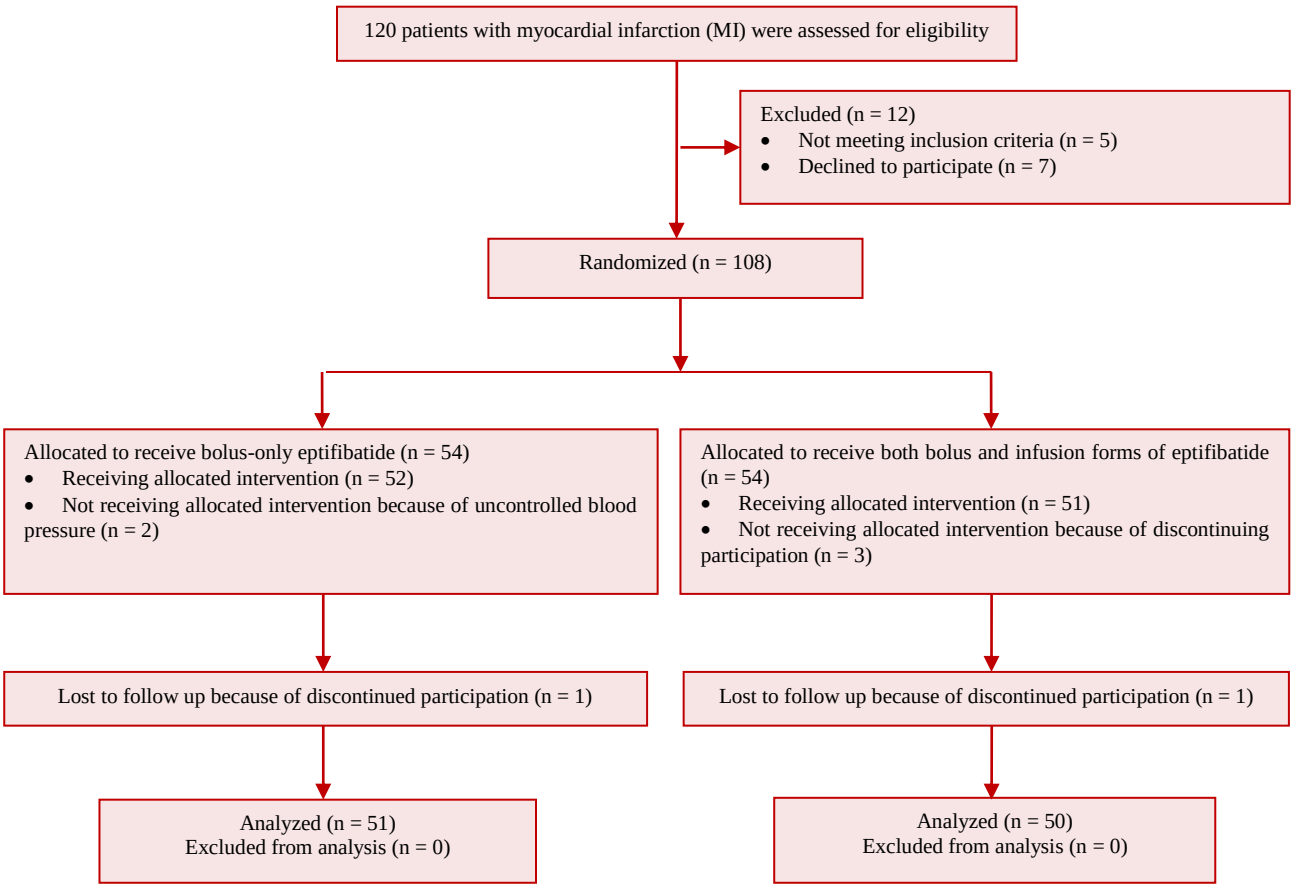

Figure 1. Participation in this study

Table 1. Clinical and laboratory measurements

Variables		Bolus-only eptifibatide (n = 51) Mean ± SD	Bolus plus infusion eptifibatide (n = 50) Mean ± SD	P*
Mean SBP during hospitalization		136.70 ± 3.90	131.67 ± 8.24	0.320
The lowest SBP		107.45 ± 2.34	107.08 ± 4.71	0.630
Mean DBP during hospitalization		84.77 ± 2.44	82.27 ± 4.63	0.510
The lowest DBP		69.52 ± 1.72	66.81 ± 2.54	0.400
Mean time duration of hemostasis (minute)		8.13 ± 0.45	16.46 ± 0.71	< 0.001
Hb	During hospitalization	13.71 ± 0.23	14.60 ± 0.32	0.470
	At discharge	13.33 ± 0.37	13.60 ± 0.78	0.660
Platelet count	During hospitalization	218.89 ± 4.72	218.17 ± 18.78	0.840
	At discharge	243.38 ± 23.96	195.00 ± 39.61	0.730
WBC	During hospitalization	8608.13 ± 559.27	10900.00 ± 1177.18	0.150
	At discharge	8924.28 ± 948.48	10951.25 ± 3844.81	0.390
BUN	During hospitalization	27.53 ± 3.30	31.83 ± 3.72	0.130
	At discharge	35.89 ± 3.92	34.20 ± 3.37	0.790
Creatinine	During hospitalization	1.10 ± 0.04	1.10 ± 0.11	0.220
	At discharge	1.07 ± 0.05	1.28 ± 0.16	0.200

* Independent t-test

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; WBC: White blood cell; BUN: Blood urea nitrogen; SD: Standard deviation

The mean level of Hb, WBC, platelet, BUN and creatinine were not different between two groups during hospitalizations and in discharge time (P > 0.050). Comparing these variables in each group between the time of hospitalization and discharge did not show any significant differences (P > 0.050) (Table 1).

Evaluating bleedings and hematoma showed that there was just 1 patient (1.96%) in the first group who had severe bleeding with hemodynamic impairment and patients in the second group did not show any bleedings (P = 0.580). About 13.72% (n = 7) in the first group and 50% (n = 25) in the second group showed hematoma in the site of angiography that most of these hematomas were < 5 cm. There was a significant difference between two groups in the presence of hematoma in the site of angiography (P = 0.030). Retroperitoneal hematoma was just occurred in 1.98% (n = 2) of participants that both of them were in the first group (P = 0.430) (Table 2).

Patients follow-up 6 months after PCI showed that about 25.5% (n = 13) of patients in the first group and 38.0% (n = 19) in the second group did not need any additional cardiovascular intervention. Among those who needed additional coronary intervention in 6 months duration after PCI, patients in the second group needed angiography and PCI and those in the first group needed angiography, PCI, stent, and even coronary artery bypass graft (CABG). Comparing these interventions between two groups did not show any statistical significant differences (P = 0.060) (Table 3).

Table 2. The prevalence of bleeding and hematomas among patients who received bolus-only from or bolus+ infusion form of eptifibatide

Variables		Bolus-only eptifibatide (n = 51) [n (%)]	Bolus plus infusion eptifibatide (n = 50) [n (%)]	P*
Bleeding	No bleeding	50 (98.03)	50 (100)	0.580
	Mild	0 (0)	0 (0)	
	Moderate	0 (0)	0 (0)	
	Severe	1 (1.97)	0 (0)	
Hematoma size (cm)	Less than 5	4 (7.84)	15 (30.00)	0.030*
	5-10	1 (1.96)	14 (7.00)	
	More than 10	2 (3.92)	3 (6.00)	
Retroperitoneal hemorrhage	Yes	2 (3.92)	0 (0)	0.430

* Fisher's exact test

Table 3. The needs for more intervention in both groups (receiving bolus-only from or bolus + infusion form of eptifibatide) after six months

Variables	Bolus-only eptifibatide (n = 51) [n (%)]	Bolus plus infusion eptifibatide (n = 50) [n (%)]	P*
No more intervention	13 (25.50)	19 (38.00)	0.060
Angiography	5 (11.11)	4 (8.00)	
Angiography + PCI	25 (55.56)	26 (52.00)	
CABG + PCI	1 (2.22)	0 (0)	
CABG + angiography	2 (4.44)	0 (0)	
Angiography + PCI + stent	5 (10.10)	0 (0)	
PCI + stent	0 (0)	1 (2.00)	

* Fisher's exact test

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft

Discussion

This study evaluated 101 patients with MI who were candidate for angiography and PCI for the effects of administrating eptifibatide in bolus and infusion forms. This study showed that although there was no difference in short-term and long-term outcomes between these two methods of administrating the medication, the prevalence of bleeding was significantly higher in those who received eptifibatide in infusion form.

Abrupt coronary artery closure after percutaneous coronary revascularization is one of the main causes of mortality and morbidity accompanied with this procedure.[12] Despite the routine use of aspirin and heparin, ischemic complications were seen in 8%-10% of cases.[13] Platelet adhesion, activation, and aggression are the key processes leading to thrombosis. The end stage of thrombosis formation is binding of fibrinogen to platelet integrin GP IIb/IIIa. GPI are medications that inhibit the end stage of this process and reduce ischemic complications after coronary interventions.[14]

This study showed that bleeding events were more probable in patients who had longer exposure to eptifibatide, although there were similar clinical outcomes between two groups. One study that evaluated eptifibatide in patients with NSTEMI showed that there were not any differences between eptifibatide and placebo in incidence of bleeding complications after PCI. In this study, the prevalence of bleedings was 2.7% and the most common type of bleeding was gastrointestinal (GI).[15] In another study on patients with unstable angina, two doses of eptifibatide were compared with placebo and there was no difference between patients in bleeding events and just minor bleeding was more prevalent in those who received any dose of eptifibatide. In addition, platelet count and need for blood transfusion was similar in all participants.[16,17] Most of the studies evaluated eptifibatide in comparison to placebo or other anti-platelet medications; also there are other studies that evaluated various doses of this medication in comparison to each other and there are limited studies comparing different methods of administrating this medication. This study compared the bolus and infusion forms of this medication, although most of the studies administrated this medication in infusion form with different doses. Fung et al. evaluated 624 patients with stable angina, ACS, and STEMI. In this study, patients were divided into two groups and received abbreviated infusion of eptifibatide (less than 2 hours) and standard infusion of eptifibatide (18 hours). In this study, bleeding events were statistically lower in those who received this medication in abbreviated form and the incidence of MI, stent thrombosis, and death 30 days after intervention was not different between groups. This study showed that prescribing eptifibatide in less than 2 hours infusion was successful, uncomplicated, and safe; and shortening infusion duration reduced bleeding events without eliminating the role of GPI.[10] Findings of this study are similar to other limited studies which evaluated the bolus-only strategy of administrating eptifibatide. Kini et al. compared the bolus-only and bolus + infusion forms of prescribing eptifibatide in patients who underwent PCI and showed significant reduction in bleeding complications and equivalent clinical outcomes with bolus-only eptifibatide method when compared with bolus + infusion strategy. It also showed that bolus-only eptifibatide could improve incidence of ambulatory PCI and reduce length of hospital stay and also it was more cost-effective in comparison to bolus + infusion strategy.[18] There is one study that is slightly different from our findings. Bertrand et al.

evaluated the bolus-only and blouse + infusion forms of Abciximab as an GPI on patients who were candidate for transradial coronary stenting and showed that the incidence of bleeding, MI, death, urgent revascularization, and repeated hospitalization was more in those who received just the bolus form of Abciximab.[11] Maybe this study has different outcomes because of using another GPI, and most of the studies which evaluated eptifibatide had similar findings to our study.

GPI can cause thrombocytopenia which increases the risk of serious bleedings. In a study evaluating 9 patients who received eptifibatide and showed thrombocytopenia, there was evidence from platelet destruction that was caused by drug dependent immunoglobulin G (IgG) antibodies. This study suggested that we could evaluate the risk of thrombocytopenia and bleeding in patients who received eptifibatide by screening patients for these antibodies.[19]

The present study suffers from a number of limitations that must be taken into account in the interpretation and generalization of these results. The sample size of this study was too small for generalizing these findings to general population and evaluating the exact differences between eptifibatide bolus only and bolus + infusion strategies and it is better to plan another study with larger sample size. Another limitation is evaluating limited variables as an outcome of this study. Further studies should consider other variables associated with these types of treatment strategies including hospital stay, and patient's satisfaction and quality of life.

Conclusion

This study showed that bolus-only eptifibatide before PCI caused significant reduction in bleeding complications and equivalent clinical and cardiovascular outcomes in comparison to bolus + infusion strategy of prescribing eptifibatide.

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None.

Conflict of Interests

Authors have no conflict of interests.

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