

Efficacy and safety of single high-dose versus double high-dose intracoronary bolus tirofiban in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Objectives: We evaluated the efficacy and safety of single high-dose versus double high-dose intracoronary bolus tirofiban in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: A total of 80 patients, who were admitted to our clinic and underwent primary PCI, were included in this observational cohort study. The patients were divided into the single high-dose group (n = 40) and the double high-dose group (n = 40) according to the intracoronary bolus tirofiban regime. The primary endpoint was assumed as the incidence of major adverse cardiac event (s) (MACE) defined as all-cause mortality and repeat coronary revascularization (target vessel revascularization [TVR]) at 30 days. MACE and bleeding events were evaluated at 7 and 30 days.

Results: The primary endpoint was not significantly different between the single and the double high-dose groups (40.0% vs. 17.5%, $p = 0.994$). However, a significantly lower 30-day TVR rate was observed in the double high-dose group (27.5% vs. 7.5%, $p = 0.019$). No significant difference was observed in terms of 30-day all-cause mortality between the two groups (12.5% vs. 10.0%, $p = 0.712$). Major bleeding events were not observed in any group. Multivariate logistic regression analysis demonstrated that CRUSADE score (Hazard ratio [HR]: 5.721; 95% CI: 2.036 to 16.073, $p = 0.001$) and platelet count (HR: 1.009; 95% CI: 1.000 to 1.018, $p = 0.048$) were the independent predictors of bleeding at 7 days.

Conclusions: Double high-dose intracoronary bolus tirofiban in STEMI patients undergoing primary PCI was associated with significantly lower 30-day TVR rates without an increase in bleeding events. However, it did not significantly affect MACE and all-cause mortality rates.

Keywords: high-dose, glycoprotein IIb/IIIa receptor inhibitor, tirofiban, ST-segment elevation myocardial infarction, efficacy, safety

ST-segment elevation myocardial infarction (STEMI) is a potentially life-threatening condition, which usually occurs as a result of a vulnerable coronary plaque rupture and thrombus formation, and consequently leads to an acute reduction in myocardial

blood flow and subsequent myocardial necrosis. However, it sometimes manifests as sudden cardiac arrest due to ischemia-induced tachyarrhythmia. It is noteworthy that the incidence of STEMI is declining [1, 2], possibly due to the reduction in smoking, the aging

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of the population, and the prevalent use of statin therapy. Similar trends have been suggested for sudden cardiac arrest. Primary percutaneous coronary intervention (PCI) is the preferred approach for early restoration of myocardial blood flow in the infarct-related artery in patients with STEMI [3]. In addition, a combination of anti-ischemic, antiplatelet and antithrombotic therapies is indispensable.

Tirofiban is a highly selective and short-acting platelet glycoprotein (GP) IIb/IIIa receptor inhibitor, which inhibits platelet aggregation by blocking the combination of fibrinogen and GP IIb/IIIa and consequently prevents myocardial ischemia caused by coronary thrombosis [4, 5]. Regarding tirofiban dosage, unlike the trials of low-dose bolus regimens [6-9], recent studies involving the high-dose bolus regimen support its efficacy in patients with STEMI undergoing primary PCI [10-12]. These results may translate to clinical benefit while not significantly increasing bleeding complications. Not only the optimal doses but also the ideal route of administration of GP IIb/IIIa receptor inhibitors has also been actively investigated [13, 14]. A previous study demonstrated that the standard intravenous tirofiban bolus plus infusion strategy was not superior to an intracoronary tirofiban bolus-only strategy with respect to improvement of microvascular perfusion after primary PCI [15]. In this study, we aimed to evaluate the efficacy and safety of single high-dose versus double high-dose intracoronary bolus tirofiban in STEMI patients undergoing primary PCI.

METHODS

Study Population and Design

This single-center, observational cohort study included a total of 80 patients, who were diagnosed with STEMI and underwent primary PCI within 12 h of the onset of symptoms at our cardiology clinic between January 2016 and June 2016. All patients meeting the inclusion criteria were included into the study consecutively. Informed written consent was obtained from all patients. Data of the patients were obtained from file archives and catheter laboratory records.

The patients in the groups were in accordance with the current guidelines for the indication of tirofiban. The

study population was divided into two groups by sequence number; the single high-dose group (n = 40) and the double high-dose group (n = 40). Depending on the sequence number, in the single high-dose group, tirofiban 25 mcg/kg via intracoronary route within 3 min followed by 0.15 mcg/kg/min via intravenous route for up to 24 h was administered, whereas in the double high-dose group, tirofiban 25 mcg/kg was administered within 3 min followed by a second dose after 5 min and 0.15 mcg/kg/min via intravenous route for up to 24 hours. Other medications were administered to all the patients according to the current best clinical practice: aspirin (loading dose of 300 mg, then 100 mg qd), clopidogrel (loading dose of 600 mg, then 75 mg qd), heparin (40-70 U/kg) or low molecular weight heparin, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), β -blocker, and statin therapy.

Patients with acute/chronic infective or inflammatory disease, severe heart valve disease, severe congestive heart failure (left ventricular ejection fraction (LVEF) < 30%), chronic kidney disease (glomerular filtration rate < 90 mL/min/1.73 m²), chronic liver disease and Killip class 3-4 were not included. The Institutional Ethics Committee approved the study protocol.

Data concerning cardiovascular risk factors, including age, gender, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HPL), and smoking status were noted. Venous blood samples to measure complete blood count, lipid panel, high-sensitivity cardiac troponin T (hs-cTnT), creatinine, and high-sensitivity C-reactive protein (hs-CRP) levels were obtained from all the patients on admission. Routine blood chemistry and lipid panel parameters were measured with a standard auto-analyzer. Blood counts were measured with a Sysmex K-1000 (Block Scientific, Bohemia, New York, USA) auto-analyzer within 5 min of sampling. Serum concentrations of hs-cTnT were measured using an Elecsys 2010 analyzer (Cobas e 411; Elecsys, Roche Diagnostics, Mannheim, Germany). Serum concentrations of hs-CRP levels were measured using an automated chemistry analyzer by a commercial kit (Abbott, Aeroset, Holliston, Minn.).

Coronary intervention procedures were performed using commercially available Siemens (Axiom Sensus XP, Berlin, Germany) and Toshiba (Infinix CSI, Tokyo,

Japan) devices via femoral access and standard techniques. Angiographic features, including initial TIMI flow, TIMI flow after tirofiban administration, final TIMI flow after PCI, no-reflow phenomenon, initial TIMI thrombus grade, and TIMI thrombus grade after tirofiban administration were evaluated by two blinded interventional cardiologists. The diagnosis of the no-reflow phenomenon was made when post-procedural TIMI flow grade is < 3 , or in the case of a TIMI flow grade of 3 when myocardial blush grade is 0 or 1, or when ST resolution within 4 h of the procedure is $< 70\%$ [16]. Coronary thrombus was graded according to the TIMI thrombus scale [17]. Patients were followed up for 30 days for major adverse cardiovascular event (s) (MACE) and target vessel revascularization (TVR). All data were recorded and there were no missing data. The cause of deaths were all cardiac, especially ventricular arrhythmia.

Clinical Endpoints and Definitions

Data regarding clinical end points were obtained from the health information system of our institute and the national health registry. No study-specific clinical follow-up was done. The primary endpoint was defined as the incidence of MACE defined as all-cause mortality and repeat coronary revascularization (target vessel revascularization [TVR]) at 30 days. TVR was defined as any revascularization procedure for stent thrombosis or in-stent restenosis, including bypass surgery, involving the initially treated artery. MACEs were evaluated at 7 and 30 days. Major bleeding was defined as an intracranial bleeding or a decrease in the hemoglobin concentration of 5 g/dL or more or a decrease in hematocrit of 15% or more. The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology / American Heart Association guidelines) score to stratify baseline risk of major bleeding was calculated. Bleeding was considered minor if the hemoglobin concentration decreased by < 5 g/dL or the hematocrit decreased by $< 15\%$ [18]. Bleeding events were evaluated at 7 and 30 days.

Statistical Analysis

Data analyses were performed using SPSS statistical software package version 20.0 (Chicago, IL, USA).

Continuous variables were expressed as mean \pm standard deviation and median and interquartile range as appropriate. Categorical variables were expressed as number and percentage. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Comparison of continuous variables between groups was performed using the Independent-Samples T test and the Mann-Whitney U test as appropriate. Comparison of categorical variables between groups was performed using the Chi-Square test and the Fisher's Exact test as appropriate. The correlation between certain variables of the treatment groups was performed using the Spearman's rank-order correlations analysis and the Pearson product-moment correlation analysis as appropriate. All significant parameters ($p < 0.01$) in the univariate analysis were selected for the multivariate model and forward stepwise multivariate logistic regression analysis was used to determine the independent predictors of bleeding at 7 days. The coefficient of regression and 95% confidence interval for each independent variable were calculated. The 30-day event-free survival curves were constructed using the Kaplan-Meier method and statistical differences between curves were assessed by the log-rank test. The hazard ratio for treatment comparisons was estimated using Cox proportional hazard models. A two-tailed p -value of less than 0.05 was considered as significant.

RESULTS

A total of 80 patients (57 men and 23 women; mean age: 59.4 ± 10.4 years), who were diagnosed with STEMI and underwent primary PCI were included. The patients were divided into the single high-dose group ($n = 40$) and the double high-dose group ($n = 40$) regarding tirofiban dose. Baseline characteristics of the patients were similar in the two groups except in terms of gender and serum creatinine levels (Table 1).

Angiographic and procedural characteristics of the patients were similar in the two groups except in terms of the initial TIMI flow, TIMI flow after tirofiban administration and stent length (Table 2). Regarding the initial TIMI flow, proportions of patients with grade 0, 1, 2, and 3 in the single high-dose group were

Table 1. Baseline characteristics of the patients

Variable	Single high-dose group (n = 40)	Double high-dose group (n = 40)	<i>p</i> ^a value
Age (years)	59.2 ± 9.7	59.7 ± 11.2	0.807
Gender, (male), n (%)	24 (60.0)	33 (82.5)	0.026
HT, n (%)	11 (27.5)	14 (35.0)	0.605
DM, n (%)	6 (15.0)	7 (17.5)	0.501
HPL, n (%)	9 (22.5)	10 (25.0)	0.523
Current smoker, n (%)	10 (25.0)	12 (30.0)	0.766
CAD, n (%)	4 (10.0)	4 (10.0)	_{-b}
CABG, n (%)	2 (5.0)	0 (0.0)	0.423
COLD, n (%)	1 (2.5)	1 (2.5)	_{-b}
Hemoglobin (g/dL)	13.0 ± 2.1	13.1 ± 2.2	0.679
WBC, ×10 ³ /uL	11.9 ± 4.9	11.0 ± 4.5	0.285
	10.25 (8.8-14.6)	9.5 (8.2-14.5)	
Hematocrit (%)	39.6 ± 6.0	41.0 ± 5.2	0.284
Platelet count, ×10 ³ /uL	285.6 ± 74.6	287.3 ± 85.0	0.992
	269 (230.5-336.8)	277 (222-321)	
Creatinine (mg/dL)	0.8 ± 0.3	0.9 ± 0.3	0.010
	0.8 (0.6-1.0)	0.9 (0.8-1.1)	
Triglyceride (mg/dL)	202.5 ± 120.6	208.5 ± 111.7	0.573
	200 (96-266.8)	212 (92-279)	
Total cholesterol (mg/dL)	213.1 ± 58.4	205.0 ± 42.6	0.456
	209.5 (174.3-245.3)	202 (184-237)	
HDL cholesterol (mg/dL)	36.5 ± 7.9	39.1 ± 10.7	0.296
	33 (30-43)	39 (32-44)	
LDL cholesterol (mg/dL)	148.8 ± 55.2	143.4 ± 27.6	0.627
	138 (127.3-158.5)	145 (128-160)	
hs-CRP (mg/dL)	2.3 ± 2.9	2.5 ± 2.2	0.324
	1.8 (0.4-3.4)	1.6 (0.8-3.7)	
hs-cTnT (ng/mL)	3.1 ± 3.1	3.1 ± 3.3	0.722
	2.2 (0.76-4.2)	1.7 (0.75-4)	
LV ejection fraction (%)	46.1 ± 11.7	48.5 ± 7.0	0.261
CRUSADE risk category, n (%)			
Very low (score ≤ 20)	6 (15.0)	8 (20.0)	
Low (score 21-30)	11 (27.5)	14 (35.0)	
Moderate (score 31-40)	14 (35.0)	8 (20.0)	0.359
High (score 41-50)	8 (20.0)	6 (15.0)	
Very high (> 50)	1 (2.5)	4 (10.0)	
Cardiovascular drugs, n (%)			
Clopidogrel	40 (100.0)	40 (100.0)	_{-b}
Aspirin	40 (100.0)	40 (100.0)	_{-b}
β blocker	38 (95.0)	37 (92.5)	0.228
Statin	40 (100.0)	40 (100.0)	_{-b}
ACE-I/ARB	40 (100.0)	40 (100.0)	_{-b}

Data are presented as number (percentage) or mean ± standard deviation or median (interquartile range). HT = Hypertension, DM = Diabetes mellitus, HPL = Hyperlipidemia, CAD = Coronary artery disease, CABG = Coronary artery bypass grafting, COLD = Chronic obstructive lung disease, WBC = White blood cell, HDL = High-density lipoprotein, LDL = Low-density lipoprotein, hs-CRP = High-sensitivity C-reactive protein, hs-cTnT = High-sensitivity cardiac troponin T, LV = Left ventricle, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines, ACEI = Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker

^aIndependent-Samples T test, Chi-Square test, Mann-Whitney U test.

^bNo statistics are computed because the variable is a constant.

Table 2. Angiographic and procedural characteristics

Variable	Single high-dose group (n = 40)	Double high-dose group (n = 40)	p ^a value
Culprit vessel, n (%)			
LAD	15 (37.5)	20 (50.0)	
LCx	9 (22.5)	8 (20.0)	
RCA	13 (32.5)	11 (27.5)	
IM	2 (5.0)	1 (2.5)	
SVG	1 (2.5)	0 (0.0)	
One vessel disease, n (%)	24 (60.0)	21 (52.5)	0.423
Multi-vessel disease, n (%)	16 (40.0)	19 (47.5)	0.374
Mean ischemic time (min)	56	61	0.459
Killip class 1	21	18	0.562
Killip class 2	19	22	0.378
Balloon pre-dilatation, n (%)	24 (60.0)	27 (67.5)	0.485
Balloon post-dilatation, n (%)	17 (42.5)	9 (22.5)	0.056
No-Reflow, n (%)	29 (72.5)	25 (62.5)	0.363
Thrombus aspiration, n (%)	11 (27.5)	11 (27.5)	_b
Initial TIMI flow, n (%)			
Grade 0	12 (30.0)	16 (40.0)	
Grade 1	16 (40.0)	10 (25.0)	
Grade 2	12 (30.0)	12 (30.0)	
Grade 3	0 (0.0)	2 (5.0)	
TIMI flow after Tirofiban, n (%)			
Grade 0	8 (20.0)	6 (15.0)	
Grade 1	13 (32.5)	8 (20.0)	
Grade 2	14 (35.0)	17 (42.5)	
Grade 3	5 (12.5)	9 (22.5)	
Final TIMI flow after PCI, n (%)			
Grade 0	4 (10.0)	2 (5.0)	
Grade 1	11 (27.5)	8 (20.0)	
Grade 2	14 (35.0)	16 (40.0)	
Grade 3	11 (27.5)	14 (35.0)	
Stent diameter (mm)	3.0 ± 0.5 3.0 (2.75-3)	3.0 ± 0.4 3.0 (2.75-3)	0.682
Stent length (mm)	24.9 ± 8.6 24 (18-28)	21.2 ± 10.2 19 (16-24)	0.005
Stent type, n (%)			
DES	30 (75.0)	27 (67.5)	0.459
BMS	10 (25.0)	13 (32.5)	
Initial TIMI thrombus grade, n (%)			
Grade 1	5 (12.5)	4 (10.0)	
Grade 2	22 (55.0)	18 (45.0)	
Grade 3	12 (30.0 %)	12 (30.0)	
Grade 4	1 (2.5)	5 (12.5)	
Grade 5	0 (0.0)	1 (2.5)	
TIMI thrombus grade after Tirofiban, n (%)			
Grade 1	11 (27.5)	14 (35.0)	
Grade 2	18 (45.0)	14 (35.0)	
Grade 3	10 (25.0)	8 (20.0)	
Grade 4	1 (2.5)	4 (10.0)	
Grade 5	0 (0.0)	0 (0.0)	

Data are presented as number (percentage) or mean ± standard deviation or median (interquartile range). LAD = Left anterior descending artery, LCx = Left circumflex artery, RCA = Right coronary artery, IM = Intermediate artery, SVG = Saphenous vein graft, MI = Myocardial Infarction, DES = Drug-eluting stent, BMS = Bare-metal stent, TIMI = Thrombolysis In Myocardial Infarction, PCI = Percutaneous coronary intervention

^aChi-Square test, Mann-Whitney U test.

^bNo statistics are computed because the variable is a constant

Table 3. Clinical events at 7 and 30 days

	Single high-dose group (n = 40)	Double high-dose group (n = 40)	HR (95% CI)	p ^a value
MACE at 7 days, n (%)				
TVR	6 (15.0)	3 (7.5)	0.387 (0.077-1.938)	0.206
Death	2 (5.0)	2 (5.0)	0.296 (0.027-3.274)	0.291
Total	8 (20.0)	5 (12.5)	0.478 (0.124-1.729)	0.195
MACE at 30 days, n (%)				
TVR	11 (27.5)	3 (7.5)	0.186 (0.037-0.945)	0.019
Death	5 (12.5)	4 (10.0)	0.756 (0.171-3.342)	0.712
Total	16 (40.0)	7 (17.5)	0.997 (0.381-2.605)	0.994

Data are presented as number (percentage). HR = Hazard ratio, CI = Confidence interval, MACE = Major adverse cardiac event(s), TVR = Target vessel revascularization.

^aLog-Rank test.

30.0%, 40.0%, 30.0% and 0.0%, respectively, and in the double high-dose group they were 40.0%, 25.0%, 30.0% and 5.0%, respectively. Nevertheless, the proportion of patients with TIMI flow grade 2 after tirofiban administration was higher in the double high-dose group than in the single high-dose group. In addition, it is noteworthy that there was more patients

with TIMI flow grade 0-1-2 (noreflow) in the single high-dose group after tirofiban administration. Moreover, shorter stents were deployed in the double high-dose group than in the single high-dose group ($p = 0.005$).

According to the Kaplan-Meier analysis, the primary endpoint was not significantly different

Table 4. Bleeding events at 7 and 30 days

	Single high-dose group (n = 40)	Double high-dose group (n = 40)	p ^a value
Bleeding at 7 days, n (%)			
Minor	5 (12.5)	5 (12.5)	- ^b
Major	0 (0.0)	0 (0.0)	- ^b
Bleeding at 30 days, n (%)			
Minor	9 (22.5)	6 (15.0)	0.390
Major	0(0.0)	0 (0.0)	- ^b

Data are presented as number (percentage).

^aChi-Square test.

^bNo statistics are computed because the variable is a constant.

between the two groups (single high-dose group: n = 16 (40.0%) vs. double high-dose group: n = 7 (17.5%); hazard ratio (HR): 0.997 (95% confidence interval [CI]: 0.381 to 2.605); log-rank test *p* = 0.994. However, analysis of the two main components of MACE revealed a significantly lower 30-day TVR rate in the double high-dose group (single high-dose group: n = 11 [27.5%] vs. double high-dose group: n = 3 [7.5%]; HR: 0.186 [95% CI: 0.037 to 0.945]; log-rank test *p* = 0.019) and a similar 30-day all-cause mortality rate in the two groups (single high-dose group: n = 5 [12.5%] vs. double high-dose group: n =

4 [10.0%]; HR: 0.756 [95% CI: 0.171 to 3.342]; log-rank test *p* = 0.712). Clinical events at 7 and 30 days are shown in Table 3.

There was no major bleeding in both groups. Minor bleeding occurred in 12.5% of the patients in each group at 7-day. Bleeding events at 7 and 30 days are shown in table 4. Forward stepwise multivariate logistic regression analysis demonstrated that CRUSADE score (HR: 5.721; 95% CI: 2.036 to 16.073, *p* = 0.001) and platelet count (HR: 1.009; 95% CI: 1.000 to 1.018, *p* = 0.048) were the independent predictors of bleeding at 7 days (Table 5).

Table 5. Independent predictors of bleeding at 7 days

	Univariate Model		Multivariate Model		
	Correlation coefficient	<i>p</i> value	HR	95% CI	<i>p</i> value
Age	0.332	0.003	-	-	-
CRUSADE score	0.484	< 0.001	5.721	2.036-16.073	0.001
Plasma hemoglobin level	-0.220	0.052	-	-	-
Platelet count	0.192	0.090	1.009	1.000-1.018	0.048
Serum creatinine level	0.271	0.016	-	-	-

HR = Hazard ratio, CI = Confidence interval, CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines

DISCUSSION

The substantial finding of our study is that, administration of double high-dose intracoronary bolus tirofiban in STEMI patients undergoing primary PCI, in addition to aspirin, heparin, and high-dose clopidogrel, was associated with lower 30-day TVR rates without leading to a significant increase in minor or major bleeding. However, it did not significantly affect MACE and all-cause mortality rates. Unlike the trials involved low-dose bolus regimens [6-9], studies involving the high-dose bolus regimen of tirofiban support its efficacy and safety in patients with STEMI undergoing primary PCI [10-12]. To the best of our knowledge, this is the first study in the literature comparing the efficacy and safety of the single high-dose versus double high-dose intracoronary bolus tirofiban in patients undergoing primary PCI.

Despite the considerable progress that has been

made recently regarding the treatment of STEMI, including modern antithrombotic therapy, thrombus aspiration, and drug-eluting stents, questions have been raised concerning the potential benefit of GP IIb/IIIa receptor inhibitor in this setting. Several studies have demonstrated that despite these treatments events associated with thrombotic occlusion during or after PCI may still occur in 4-12.8% of the patients, and in high-risk patients, these events occur more often [19, 20]. Tirofiban is a potent, competitive and inhibitor GP IIb/IIIa with a high specificity and affinity for the GP IIb/IIIa receptor [21]. It is a small and nonpeptide tyrosine derivative that dissociates from the GP IIb/IIIa receptor relatively rapidly, with a half-life of 2-4 hours, and its action is therefore reversed within hours after the completion of the infusion [22]. Such reversibility may have significant implications with regard to bleeding, particularly in patients who are considered for

emergent cardiac surgery.

The utility of tirofiban in patients with STEMI has been investigated in several trials [6, 10, 11, 23-25]. These studies have evaluated both the 10 mcg/kg bolus and the high-dose bolus regimens. Administration of GP IIb/IIIa receptor inhibitors for bail-out therapy where there is an angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication in patients with STEMI is a class IIa indication according to the diary guideline of the European Society of Cardiology [26]. Large studies show that in the real-world practice, GP IIb/IIIa receptor inhibitors are approximately given to 25-30% of patients with STEMI, often for bail-out situations [27, 28]. However, they should not be always restricted to patients with complications after PCI, even in the setting when high-dose clopidogrel is already given in advance of PCI because the maximum antiplatelet effect of 600 mg clopidogrel is achieved only after 2-4 h. Recent studies suggest that the high-bolus dose of tirofiban results in optimum platelet aggregation in most patients very early after PCI [23, 29]. Early administration of GP IIb/IIIa receptor inhibitors has actually attributed to the improvement in post-procedural myocardial perfusion and reduction in clinical outcomes, including death and cardiogenic shock [30, 31].

The results of several studies involving early administration of tirofiban in patients undergoing primary PCI utilizing the 10 mcg/kg bolus regimen have suggested potential benefits regarding the restoration of blood flow in the infarct-related artery and myocardial perfusion, although no improvement was found in clinical outcomes [6-8, 32]. The On-TIME 2 trial [11], was the first study to determine the benefits of pre-hospital administration of tirofiban utilizing high-dose bolus regimen in addition to dual antiplatelet therapy measured by ST-segment deviation resolution. In this study, mean residual ST deviation before PCI and 1 h after PCI was significantly lower in patients pretreated with high-bolus dose tirofiban than in those given placebo. Although, the rate of major bleeding did not differ significantly between the two groups. In addition, the results of 30-day follow-up demonstrated a significant benefit favoring tirofiban regarding the combined incidence of death, recurrent myocardial infarction, urgent TVR or thrombotic bailout. Moreover, further

analysis suggested a relationship between the level of residual ST-segment deviation and mortality. Thus, On-TIME 2 trial has demonstrated a benefit of high-dose bolus regimen of tirofiban over placebo with respect to clinical outcomes. Indeed the results of our study concerning TIMI flow before PCI and TVR rates at 30 days favoring not only the high-dose bolus regimen of tirofiban but also highlighting the potential benefits of double high-dose bolus regimen, without an increase in bleeding events.

In our study, triple antiplatelet therapy, with double high-dose bolus regimen of tirofiban, high-dose clopidogrel (600 mg) and aspirin pretreatment was not associated with an increased risk of major bleeding. This finding might be related to a very careful heparin-dose protocol at our catheterization laboratory where we only give extra heparin during complex PCI procedures which exceed 1 hour in duration. Furthermore, low-molecular-weight heparin was directly discouraged after completion of the tirofiban infusion except for patients with atrial fibrillation and prosthetic heart valve with an international normalized ratio less than 2.

Agents inhibiting platelet functions would be associated with an increased risk of bleeding. As it is well known, bleeding complications in patients undergoing PCI have been associated with an increased morbidity and mortality [33]. Therefore, preventing excessive bleeding is critical. Although it has been suggested that early initiation of a GP IIb/IIIa receptor inhibitor in patients with acute coronary syndrome may lead to an increase in bleeding [34], this was not observed in either the On-TIME 1 or the On-TIME 2 trials. Nevertheless, the results of On-TIME 2 trial revealed that there was no excess in major bleeding, even in patients receiving pre-hospital high-dose bolus tirofiban in addition to high-dose clopidogrel.

In our study, the rate of target vessel revascularization (TVR) at 30 days looks very high (27.5%) in the single high-dose group, because no-reflow was more in single high-dose group, stent length was longer in single high-dose group. We attribute the difference in the value of TVR to these reasons.

Limitations

Our study has limitations that warrant

consideration. First, this was a single-center observational study with a small number of patients. A multi-center study involving more patients could have more significant results and data. Second, our results may not apply to patients with renal insufficiency since they were not included.

CONCLUSION

Double high-dose intracoronary bolus tirofiban regimen in STEMI patients undergoing primary PCI was associated with significantly lower 30-day TVR rates without an increase in bleeding events. However, it did not significantly affect MACE and all-cause mortality rates.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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