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Research Article
Efficacy and Safety of Bivalirudin Plus Half/Full Dose of Tirofiban in Patients Undergoing Emergency Percutaneous Coronary Intervention

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Abstract

Background and Objective: A combination of bivalirudin and tirofiban is commonly applied in percutaneous coronary intervention (PCI). This study was conducted to evaluate the safety and efficacy of bivalirudin plus half/full dose of tirofiban in perioperative treatment of PCI. **Methodology:** The patients with acute coronary syndrome (ACS) undergoing PCI between January, 2013 and December, 2016 were investigated. Five hundred and twenty-five patients were divided into bivalirudin+a half dose of tirofiban group (half dose group) and bivalirudin+a full dose of tirofiban group (full dose group). The efficacy index was evaluated by thrombolysis in myocardial infarction (TIMI) flow grade, the cardiac function, major adverse cardiovascular events (MACE). The safety index was evaluated by bleeding events after PCI. Data were analyzed by SPSS software. Continuous variables were statistically analyzed by Student's t-test. Categorical variables were assessed by chi-square analysis. **Results:** The improvements of TIMI flow, cardiac function and the decreased incidence rates of MACE were shown no significant differences between the two groups. The occurrences of bleeding events in 4, 48 and 96 h, 30 and 90 days in half dose group were obviously lower than full dose group after PCI ($p<0.001$). **Conclusion:** This study revealed that half dose of tirofiban based treatment has the similar therapeutic effect and higher safety compared with full dose of tirofiban based treatment in patients with ACS undergoing emergency PCI.

Key words: Bivalirudin, tirofiban, acute coronary syndrome, percutaneous coronary intervention, safety, efficacy

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a commonly performed procedure in patients with acute coronary syndrome (ACS). Anticoagulation therapy is imperative to prevent adverse ischemic events during and after PCI[1]. Bivalirudin, a synthetic 20 amino acid polypeptide direct thrombin inhibitor, has been recommended as a class I or II anticoagulant drug in a series of PCI guidelines currently[2, 3].

However, stent thrombosis could be induced by heavy thrombus burden in lesion vessels occasionally with bivalirudin treatment[4]. The previous studies indicated that the incidences of stent thrombosis events were 2.5, 1.1 and 3.4% within 30 days in full dose bivalirudin group[5-7], which suggested that drug combination is needed to ameliorate the risks. A combination of bivalirudin and tirofiban, is commonly applied in clinical treatments to reduce the risks. Tirofiban, as the glycoprotein IIb/IIIa inhibitor, prevents platelet aggregation by blocking the conjunction of fibrinogen and receptor. The combination of conventional drug and tirofiban would provide more comprehensive and powerful anti-thrombotic effects[8]. While, no clear data has been supported for choosing a safer and more effective dose of tirofiban in the existing available guidelines and researches. The aim of the current study was to investigate a more appropriate dose of bivalirudin based therapy by comparing bivalirudin plus a full dose of tirofiban group with bivalirudin plus 1/2 of full dose of tirofiban group in patients with ACS undergoing PCI.

MATERIALS AND METHODS

Subject: The study was approved by Institutional Ethical Committees of Traditional Medicine Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Military Region General Hospital and First Affiliated Hospital of Xinjiang Medical University. Written informed consent was obtained from each patient before the surgical procedures and for the use of personal information for research purposes. The data was collected from the data centers of the hospitals.

Patients with ACS undergoing emergency PCI in Traditional Medicine Hospital of Xinjiang Uygur Autonomous Region, Xinjiang Military Region General Hospital, First Affiliated Hospital of Xinjiang Medical University between January, 2013 and December, 2016 were retrospectively investigated. Patients with heavy thrombus burden were eligible for enrollment. Heavy thrombus burden was defined as: (1) An angiographic thrombus with the greatest linear dimension more than 3 times the reference lumen diameter, (2) Cutoff pattern (lesion morphology with an abrupt cutoff without taper before the occlusion), (3) Presence of accumulated thrombus (>5 mm of linear dimension) proximal to the occlusion, (4) Presence of floating thrombus proximal to the occlusion, (5) Persistent contrast medium distal to the obstruction and (6) Reference lumen diameter of the infarct-related artery (IRA) >4.0 mm[9]. The inclusion criteria were[2,3]: (1) ST segment elevation myocardial infarction (STEMI), (2) High risk of non-ST segment elevation myocardial infarction (NSTEMI), (3) The duration from chest pain to percutaneous transluminal coronary angioplasty (PTCA) $\leq$12 h and thrombus burden couldn't be reduced with bivalirudin treatment. Patients were excluded if one or more of the following criteria were met[2,3]: (1) Age >80 or <18 years old, (2) Administration of unfractionated heparin 4 h before PCI or long-term treatment of warfarin, (3) Prior received thrombolytic therapy within 12 h before PCI, (4) Bleeding tendency including a history of gastrointestinal bleeding within 3 months, cerebral hemorrhage within 6 months, cerebral infarction within 3 months, (5) Serious agranulocytosis and thrombocytopenia, or heparin-induced thrombocytopenia, (6) Serious hepatorenal function insufficiency, (7) The lack of baseline information and (8) TIMI grade III after bivalirudin treatment.

Medicine: Bivalirudin was purchased from Shenzhen Xin Li Tai Pharmaceutical Co., Ltd. Tirofiban was purchased from Yuanda Medicine Co., Ltd, China. Low molecular weight heparin sodium was purchased from Sanofi pharmaceutical company, France.

Treatment: Patients met the inclusion criteria were retrospectively divided into two groups: bivalirudin+1/2 of full dose of tirofiban group (half dose group), bivalirudin+a full dose of tirofiban group (full dose group). All the patients received oral aspirin with 300 mg and clopidogrel with 600 mg within 6 h before surgery. Intravenously injection of bivalirudin with 0.75 mg kg^{-1} was conducted before the first angiography, followed by continuous intravenous pumping of bivalirudin with 1.75 mg kg^{-1} h^{-1} till 3-4 h later after PCI. Patients of full dose group received tirofiban with 10 μg kg^{-1} by intracoronary injection during PCI, followed by intravenous drip with 0.15 μg kg^{-1} min^{-1} continuously for 36 h. Patients in half dose group received tirofiban with 5 μg kg^{-1} by intracoronary injection during PCI, followed by intravenous drip of 0.075 μg kg^{-1} min^{-1} continuously for 36 h. All the patients received low molecular weight heparin sodium by subcutaneous injection (0.5 mg kg^{-1}) once for 12 h in 72 h after finishing the infusion of bivalirudin.

All of the patients received second angiography 15-20 min later after intracoronary injection of tirofiban to evaluate TIMI flow grades. Patients within TIMI grade III would receive comprehensive treatments. Rapamycin eluting stents would be implanted in lesion vessels, when angiography results indicated that thrombus burdens were reduced or disappeared. Patients with left main coronary artery diseases needed to receive intra-aortic balloon pump instead of stent implantation.

Therapeutic efficacy evaluation: (1) Evaluating TIMI flow grades by same experienced operators after intracoronary injection. TIMI Grade 0: No perfusion. No antegrade flow beyond the point of occlusion. Grade I: Penetration without perfusion. Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence. Grade II: Partial perfusion. Contrast material passes across the obstruction and opacifies the coronary distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or/both) are perceptibly slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel. Grade III: Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery[10-12]. (2) Major adverse cardiovascular events (MACE) within 30 and 90 days after PCI: All-cause mortality, stent thrombosis, stroke, reinfarction. (3) Cardiac function parameters: Ventricular end diastolic diameter (LVD) and left ventricular ejection fraction (LVEF) were evaluated before coronary angiogram (CAG) and 48 h, 30 days after PCI. LVEF was measured by modified Simpson method.

Safety evaluation: The bleeding event was assessed within 4, 48 and 96 h, 30 and 90 days according to the criteria of Bleeding Academic Research Consortium (BCRC)[13] . The BARC type 0: No bleeding; BARC type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization or treatment; BARC type 2: Any overt, actionable sign of hemorrhage requiring nonsurgical, medical intervention or hospitalization, prompting evaluation; BARC type 3a: Overt bleeding plus hemoglobin drop of 3-5 g dL^{-1}. Any transfusion with overt bleeding; BARC type 3b: Overt bleeding plus hemoglobin drop 5 g dL^{-1}. Cardiac tamponade bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), bleeding requiring intravenous vasoactive agents; BARC type 3c: Intracranial hemorrhage. Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision; BARC type 4: CABG-related bleeding; BARC type 5: Fatal bleeding.

Statistical analysis: Data were analyzed by SPSS software (version 16.0, SPSS, Inc, Chicago, IL)[14]. Continuous data were expressed as Means±Standard Deviation. Continuous variables were statistically analyzed by Student's t-test. Categorical variables were assessed by chi-square analysis. $p<0.05$ was considered as a statistical significance.

RESULTS

Baseline characteristics: Five hundred and twenty-five patients were included in this study (number, full dose group: 267; half dose group: 258). The baseline characteristics of the patients illustrated in Table 1 were shown with no significant differences between the two groups.

Evaluation of TIMI flow grade: The evaluation of TIMI flow grade is displayed in Table 2. No significant differences were observed between the two groups before and after using tirofiban.

Evaluation of MACE within 30 and 90 days after PCI: According to the all-cause mortality events depicted in Table 3, there were no significant differences between the two groups within 30 and 90 days.

According to stent thrombosis events shown in Table 3, no differences between the two groups were observed ($p>0.05$).

The numbers of patients with stroke and reinfarction were also displayed with no markedly differences between groups within 90 days after surgery ($p>0.05$, Table 3).

Evaluation of cardiac function: There were no significant differences between the two groups in LVD and LVEF before coronary angiogram, within 48 h after PCI and 30 days after PCI (Table 4).

Results of safety evaluation: The BARC type 1 bleeding event was shown with significant differences between groups within 4, 48 and 96 h, 30 and 90 days after PCI ($p<0.01$, Table 5). The BARC type 2-5b bleeding events were displayed with no significant differences between groups within 90 days. Totally, the bleeding events in half dose group were obviously lower than in full dose group within 4, 48 and 96 h, 30 and 90 days after PCI ($p<0.001$).

Table 1: Baseline data of the patients in full dose and half dose group

Variables	Full dose group (n = 267)	Half dose group (n = 258)	p-value
Age (years)	67.07±11.79	65.77±12.69	0.2243
Male (n, %)	202 (75.7%)	180 (69.8%)	0.1294
Diabetes (n)	50 (18.73%)	44 (17.1%)	0.6996
Hypertension (n, %)	171 (64.0%)	154 (59.7%)	0.3486
Smoking history (n, %)	177 (72.2%)	179 (69.4%)	0.5069
Peripheral arterial disease (n, %)	145 (54.3%)	140 (54.3%)	0.9381
Hyperlipoidemia (n, %)	160 (59.9%)	148 (57.4%)	0.3599
Creatinine	89±6.7	90±6.3	0.0789
Creatine kinase	1397.3±57.2	1386.4±60.5	0.343
Killip grade≥II	29 (10.9%)	32 (12.4%)	0.6782
LVEF (%)	42.1±5.29	42.3±5.36	0.6672
Systolic pressure (mm Hg)	153±7.82	154±6.98	0.1232
Diastolic pressure (mm Hg)	79±11.7	81±12.0	0.0537
STEMI (n, %)	165 (61.8%)	147 (57%)	0.3003
NSTEMI (n, %)	112 (41.9%)	113 43.8%)	0.7337
Number of lesion vessels (n, %)			
Single-vessel lesion (n, %)	198 (74.2%)	193 74.8%)	0.9439
Double-vessel lesion (n, %)	61 (22.9%)	59 22.9%)	0.9219
Three-vessel lesion (n, %)	8 (3%)	6 (2.3%)	0.8369
Culprit vessel (n, %)			
Left anterior descending (n, %)	141 (52.8%)	121 (46.9%)	0.2053
Circumflex artery (n, %)	37 (13.9%)	42 (16.3%)	0.5133
Right coronary artery (n, %)	89 (33.3%)	95 (36.8%)	0.4557
Temporary pacemaker implantation (n, %)	5 (1.9%)	7 (2.7%)	0.7247
CRUSADE bleeding scores	21.2±10.3	21.7±11.2	0.5945
CRUSADE bleeding scores 30 (Medium or high risk of bleeding event) (n, %)	45(16.9%)	42 (16.3%)	0.9524

Data are expressed as Mean±SD or number (percentage) as appropriate. Full dose group: bivalirudin+a full dose of tirofiban group, Half dose group: bivalirudin+1/2 of full dose of tirofiban group, LVEF: Left ventricular ejection fraction, STEMI: ST segment elevation myocardial infarction, NSTEMI: Non-ST-segment elevation myocardial infarction

Table 2: Comparison of TIMI flow before tirofiban and 15-20 min later after received tirofiban with the two groups

	Before tirofiban (n, %)			15-20 min later after received tirofiban (n, %)			
Groups	Grade 0	Grade I	Grade II	Grade 0	Grade I	Grade II	Grade III
Full dose group (n = 267)	9 (3.4%)	32 (11.9%)	226 (84.6%)	0	4 (1.5%)	45 (16.9%)	218 (81.7%)
Half dose group (n = 258)	10 (3.9%)	39 (15.1%)	209 (81%)	0	4 (1.6%)	51 (19.8%)	203 (78.7%)
p-values	0.9393	0.3569	0.3225	1.000	0.7585	0.4530	0.4576

Data are expressed as number (percentage), TIMI: Thrombolysis in myocardial infarction

Table 3: Occurrence of MACE in 30 and 90 days after PCI

	MACE							
	MACE in 30 days				MACE in 90 days			
Groups	All-cause death (n, %)	Stent thrombosis (n, %)	Reinfarction	Stroke	All-cause death (n, %)	Stent thrombosis (n, %)	Reinfarction	Stroke
Full dose group (n = 267)	6 (2.5%)	1 (0.37%)	1 (0.37%)	2 (0.75%)	7 (2.6%)	1 (0.37%)	1 (0.37%)	2 (0.75%)
Half dose group (n = 258)	5 (1.9%)	1 (0.39%)	2 (0.78%)	2 (0.78%)	5 (1.9%)	1 (0.39%)	2 (0.78%)	2 (0.78%)
p-values	0.9542	0.4938	0.9762	0.6401	0.8165	0.4938	0.9762	0.6401

Data are expressed as number (percentage). MACE: Major Adverse Cardiovascular Events

Table 4: Comparison of cardiac function with LVD (mm) and LVEF (%) before CAG, 48 h and 30 days after PCI

	Before CAG		48 h after PCI		30 days after PCI	
Groups	LVD (mm)	LVEF (%)	LVD (mm)	LVEF (%)	LVD(mm)	LVEF (%)
Full dose group (n = 267)	51.15±6.78	42.10±5.29	53.14±6.98	45.1±4.69	53.27±6.44	47.21±5.27
Half dose group (n = 258)	50.22±6.02	42.30±5.36	52.65±6.86	44.3±4.76	53.92±6.38	46.32±5.66
p-values	0.0975	0.6672	0.4178	0.0530	0.2460	0.0627

Data are expressed as Mean±SD or as number (percentage). LVD: Left ventricular end diastolic diameter, LVEF: Left ventricular ejection fraction

Table 5: Comparison of bleeding events within 4, 48 and 96 h, 30 and 90 days after PCI

Time	Groups	Type 1	Type 2	Type 3a	Type 3b-5b	Total
Within 4 h	Full dose group	30 (11.2%)	4 (1.50%)	1 (0.37%)	0	35 (13.1%)
	Half dose group	6 (2.3%)	2 (0.78%)	0	0	8 (3.1%)
	p-value	<0.01	0.4938	0.9863	1.000	<0.01
Within 48 h	Full dose group	30 (11.2%)	4 (1.50%)	1 (0.37%)	0	35 (13.1%)
	Half dose group	6 (2.3%)	2 (0.78%)	0	0	8 (3.1%)
	p-value	<0.01	0.4938	0.9863	1.000	<0.01
Within 96 h	Full dose group	31 (11.6%)	4 (1.50%)	1 (0.37%)	0	36 (13.5%)
	Half dose group	6 (2.3%)	2 (0.78%)	0	0	8(3.10%)
	p-value	<0.01	0.4938	0.9863	1.000	<0.01
Within 30 days	Full dose group	31 (11.6%)	4 (1.50%)	1 (0.37%)	0	36 (13.48%)
	Half dose group	7 (2.7%)	2 (0.78%)	0	0	9 (3.49%)
	p-value	<0.01	0.4938	0.9863	1.000	<0.01
Within 90 days	Full dose group	31 (11.6%)	4 (1.50%)	1 (0.37%)	0	36 (13.48%)
	Half dose group	7 (2.7%)	2 (0.78%)	0	0	9 (3.49%)
	p-value	<0.01	0.4938	0.9863	1.000	<0.01

Data are expressed as Mean±SD or as number (percentage)

DISCUSSION

The study represented contemporary therapeutic and safety evaluations of thrombin inhibitor bivalirudin with different doses of GP IIb/IIIa inhibitor tirofiban in patients with ACS. The PCI is a standard care for patients with ACS, which could further increase the risk of acute intracoronary thrombosis by disrupting the coronary endothelium, leading to vessel closure during or soon after the procedure[15]. Therefore, most international guidelines recommended adjunctive antithrombotic treatments of anticoagulant and antiplatelet agents for PCI[2,16,17]. A combination of bivalirudin and tirofiban for anticoagulation and anti-platelet aggregation strategies, could decrease the risk for stent thrombosis.

The study of HORIZONS-AMI trial[5] with the increasing incidence rate of stent thrombosis in patients with bivalirudin treatment differs from this study, which may relate to different antithrombotic therapies. In this study, 600 mg clopidogrel's onset time can be delayed up to 2-6 h later after oral therapy. The half-life period of bivalirudin lasts for 25 min, thrombin activity will be restored fairly rapidly when bivalirudin is stopped immediately after PCI.[18] Therefore, bivalirudin was continually provided till 4 h later after PCI to keep antithrombotic effect until the oral medication worked. Additional full dose or half dose of tirofiban would be chosen for intensive therapy in patients with heavy thrombus burden. These studies showed that thrombosis events could be controlled well in both groups, which was consistent with the study by Lin *et al.*[19] Meanwhile, the occurrence rate of stent thrombosis was shown with no significant difference between the two groups, which indicated that the half dose of tirofiban based therapy had the similar effect in reducing ischemia events compared with full dose of tirofiban based therapy.

Tirofiban, as an adjunct to PTCA, coronary stenting and in combination with fibrinolytic therapy, has been studied in the medical management of ACS[20]. Abundant researches indicate that a full dose of tirofiban could increase TIMI flow[21-23]. Lin *et al.*[19] observed similar results of TIMI flows in full and half dose of tirofiban groups. Consistently, by comparing full dose of tirofiban group with half dose of tirofiban group in TIMI flow grade before and after PCI, the TIMI flow were obviously increased in both groups and no significant difference was occurred between the two groups after PCI, which indicated that half dose of tirofiban based therapy could reach the reperfusion of infarct arteries and had the similar antithrombotic effect compared with full dose of tirofiban based therapy.

Cardiac function is an important indication to evaluate antithrombotic effect[24,25]. Effective antithrombotic therapy could improve left ventricular function by cardiac effective reperfusion. Present study demonstrated that the LVD of both groups were increased in 48 h and 30 days after the operation. The risk of ventricular remodeling after myocardial infarction was excluded due to the improvement of LVEF, which indicated better left ventricular systolic function in both groups. No statistical differences of LVEF, LVD during perioperative period between two groups indicated that the half dose of tirofiban with bivalirudin is sufficient to improve microcirculation and reperfusion.

In the present study, no significant differences were obtained between the two groups in the occurrences of all-cause mortality, stent thrombosis, stroke and reinfarction, indicating that half and full dose of tirofiban had similar effects on postoperative MACE occurrence.

According to bleeding events in both groups, half dose of tirofiban has an apparently advantage in reducing the risk of bleeding than full dose of tirofiban. It was observed that most bleeding events were occurred in 48 h after the operation

(the high incidence stage in bleeding event). The bleeding event in both groups all belonged to BARC type 1 bleeding (equalling to hyporrhea in TIMI scale) such as cutaneous hemorrhage, gingival hemorrhage. Obvious differences were shown between the two groups within 90 days after PCI ($p<0.01$). The BARC type 2 and 3a bleeding events only could be found in full dose group with gastrointestinal hemorrhage. BARC type 3b-5 bleeding events were not observed in these patients. Previous studies of bivalirudin treatment in bleeding event showed lower occurrence rate compared with unfractionated heparin and most bleeding events were BARC type 1 bleeding or hyporrhea in TIMI scale, which was consistent with this study[26,27]. The occurrence rate of BARC type 1 bleeding study in low dose group of tirofiban by Lin *et al.*[19] was 2.9%, which was similar with the result of 3.0% in the half dose group. The rate was much higher of 11% in the full dose group, which is similar with the result of 12% in bivalirudin+unfractionated heparin group in the randomized efficacy study of tirofiban for outcomes and restenosis (RESTORE) research[28]. Therefore, the additional half dose of tirofiban has a great superiority in reducing bleeding event and the occurrence rate of relevant MACE incidents, improving the safety of antithrombotic therapy.

This study has several limitations. First limitation in this study was the retrospective study with limited data. Another limitation can be considered with additional groups. In this study, two different doses of tirofiban groups were displayed. More groups should be preferred to investigate the most appropriate therapy.

CONCLUSION

Half dose of tirofiban based treatment has the similar therapeutic effect and less bleeding events, without increased occurrence rate of MACE incidents compared with full dose of tirofiban based treatment in patients with ACS undergoing PCI, indicating that it might be a safer antithrombotic therapy in perioperative treatment of PCI.

SIGNIFICANCE STATEMENT

The study discovers the more preferable dose of tirofiban that can be benificial for clinical use. In this study, it is found that half dose of tirofiban based treatment has the similar therapeutic effect and higher safety compared with full dose of tirofiban based treatment in patients with ACS undergoing emergency PCI. This study will help the researchers to uncover the critical areas of dosage selection that many researchers were not able to explore. Thus, a new theory on the appropriate dose of tirofiban may be applied in clinical treatments.

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