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Efficacy and Safety of Bivalirudin versus Heparin Plus Tirofiban in Elderly Patients with Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract

Objective: The aim of this study was to investigate the antithrombotic effect and safety of Bivalirudin compared with heparin plus Tirofiban in elderly patients with acute myocardial infarction undergoing primary Percutaneous Coronary Intervention (PCI).

Methods: One hundred and twenty elderly patients were randomly assigned to receive two different antithrombotic therapies (Group A: Bivalirudin alone or Group B: Heparin plus Tirofiban) in a 1:1 ratio according to the treatment sequence and a table of random numbers. The clinical information, routine examination results, infarct-related sites of the enrolled patients were recorded, and the Thrombolysis in Myocardial Infarction (TIMI) flow grade and other safety indexes after PCI were analyzed.

Results: No statistically significant differences existed in ST-segment depression at 2 h after intervention, post-PCI TIMI flow grade and reduction of N-terminal pro-B type natriuretic peptide (NT-proBNP) serum concentrations in patients on day 7 versus day 1 after PCI between the two groups ($P>0.05$). However, the adverse clinical events of bleeding showed significant differences in the two groups ($P<0.05$).

Conclusion: Bivalirudin exerts confirmed anticoagulant effect and indicates lower risk of bleeding compared with heparin plus Tirofiban in elderly patients with acute myocardial infarction undergoing primary PCI.

Keywords: Bivalirudin; Heparin; Tirofiban; Percutaneous coronary intervention; Efficacy

Introduction

Percutaneous Coronary Intervention (PCI), a therapy that can improve myocardial blood supply using cardiac catheterization technique to dilate stenotic or occlusive coronary arteries, performs relative small trauma and low risk [1,2]. Antithrombotic drugs are needed for the patients before and after PCI. Heparin, as the first choice of commonly used drugs in the past, has displayed rapid and obvious effect. Nevertheless, heparin has several well-established limitations, including unpredictable anticoagulant effect and high bleeding risk [3]. Bivalirudin, a new anticoagulant drug, can bind with thrombin directly, specifically and reversibly, and shows better efficacy, safety and tolerance compared with heparin [4]. Moreover, bivalirudin has been widely used in clinical as an anticoagulant therapy [5,6] including Percutaneous Coronary Artery forming (PTCA), Unstable Angina Pectoris (UAP), Acute Coronary Syndrome (ACS) and Myocardial Infarction (MI), peripheral artery interventional therapy, major heart surgery, heart-lung transplantation and so on and high rank recommendations by correlation guide and so on ACC, ESC [7,8]. The current study aims to evaluate the antithrombotic effect and safety of Bivalirudin compared with Heparin plus Tirofiban in 120 elderly patients with acute ST-Segment Elevation Myocardial Infarction (STEMI) undergoing primary PCI.

Methods

Study population

One hundred and twenty consecutive elderly patients (93 men and 27 women) aged from 60 to 82 years (mean ± SD, 70.98 ± 4.06 years), The time of onset to PCI was less than 12 hours, who were hospitalized in Department of Cardiology, Xuzhou Hospital Affiliated East South University School of Medicine from February 2013 to August 2015 because of STEMI undergoing primary PCI, were enrolled. Patients were randomly assigned to receive two different antithrombotic therapies (Group A: bivalirudin alone or Group B: heparin plus tirofiban) in a 1:1 ratio according to the treatment sequence and a table of random numbers. The enrolled patients were eligible for STEMI diagnostic criteria of American College of Cardiology (ACC) and European Society of Cardiology (ESC). Exclusion criteria included previous or current serious heart, liver, renal or other critical organ failures, neurological or psychiatric diseases, major surgery or trauma history, systemic infection, patients in the menstrual period, pregnancy, lactation and other special populations. All patients provided written informed consent before randomization.

Treatment

Patients in the two groups were treated with the same routine support therapy. All patients were pretreated before intervention with aspirin (300 mg) and clopidogrel (600 mg). For Group A, bivalirudin was given as an intravenous bolus of 0.75 mg/kg before intervention,

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followed by infusion of 1.75 mg/kg/h during the PCI procedure and for 4 hours afterwards. For Group B, heparin 100 U/kg (maximum dose was 10000 U) and tirofiban 10 μg/kg boluses were given before intervention, followed by a 0.75 μg/kg/min tirofiban infusion during the PCI procedure and for 36 hours afterwards. After the PCI, additional low-molecular-weight heparin (5000U, 2 times/day for 7 days) was administered as a subcutaneous injection, aspirin 100 mg/day and clopidogrel bisulfate 75 mg/day were administered orally. Other cardiovascular medications, such as statins, beta blockers or nitrates, were given in accordance with the patient's condition. All interventions were performed with the same equipment's and operators.

End points and definitions

General information, medical history, routine physical examination, including blood lipids, blood glucose, blood pressure, routine blood test, hemoglobin of all patients were recorded. All patients were observed until seven days after PCI. Taking Thrombolysis in Myocardial Infarction (TIMI) flow grades as main indexes of the clinical evaluation. The sites of myocardial infarction and TIMI flow grades in the infarct-related artery were obtained. And the rates of ST-segment depression were measured at 2h after PCI. The electrochemical luminescence immunity analysis method was used to detect the reduction of N-terminal pro-B type natriuretic peptide (NT-proBNP) serum concentrations in patients on day 7 versus day 1 after PCI to evaluate statistically significant differences between the two groups in the myocardial perfusion level and the improvement of cardiac function. Bleeding is the main safety indexes and any bleeding as defined by the Bleeding Academic Research Consortium (BARC) definition was observed.

Statistical analysis

All calculations were performed by SPSS 17.0. Numerical values were expressed as mean ± SD and analyzed with t-test between the Group. Median with interquartile range (IQR) Q50 (Q25Q75)) were reported when the data are not normally distributed. Log-transformation was applied before using the t-test to compare the two groups. Categorical variables were expressed as percentage and compared using the χ^2 test. Fisher's exact tests were used to compare two categorical variables when expected numbers are small. A value of $P<0.05$ was considered statistically significant.

Results

Clinical characteristics

The baseline characteristics of this study population are indicated in Table 1. No statistically significant differences were observed in age, gender, medical history, infarct-related artery and clinical examinations between the two randomization groups.

Treatment and procedural characteristics

Bivalirudin significantly reduced the rates of hemoptysis and Bleeding Academic Research Consortium (BARC) type 2 bleeding in patients with acute myocardial infarction undergoing primary PCI, compared with heparin plus tirofiban ($P<0.05$, Table 2).

Discussion

Heparin plus Tirofiban has been commonly used as the antithrombotic therapy during PCI in clinical. Heparin can accelerate

Characteristic	Bivalirudin (n=60)	Heparin Plus Tirofiban (n=60)	t or x^2	*P*
Gender, male/female	48/12	45/15	0.05	>0.05
Age (yr)	71.34 ± 4.03	70.73 ± 3.58	0.40	>0.05
Diabetes mellitus	18	19	0.04	>0.05
Smoking history	21	22	0.04	>0.05
T (onset to pci)	5.52 ± 0.90	5.63 ± 0.97	0.22	>0.05
Clinical examination				
Hemoglobin (g/L)	120 ± 12	119 ± 14	0.42	>0.05
Dyslipidemia	46	47	0.05	>0.05
TC (mmol/L)	6.48 ± 1.23	6.42 ± 1.32	0.26	>0.05
TG (mmol/L)	1.96 ± 0.98	1.97 ± 1.02	0.05	>0.05
LDL (mmol/L)	3.63 ± 1.03	3.62 ± 1.23	0.05	>0.05
HDL (mmol/L)	1.02 ± 0.42	1.03 ± 0.53	0.11	>0.05
Hypertension	43	44	0.04	>0.05
Infarct-related site				
Anterior MI	31	28	0.30	>0.05
Un-anterior MI	29	32	0.30	>0.05
Infarct-related artery				
LAD	23	21	0.14	>0.05
LCX	18	23	0.93	>0.05
RCA	19	16	0.36	>0.05
TC: Total Cholesterol; TG: Triglyceride; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; LAD: Left Anterior Descending; LCX: Left Circumflex Coronary Artery; RCA: Right Coronary Artery.				

Table 1: Baseline characteristics.

Characteristic	Bivalirudin (n=60)	Heparin Plus Tirofiban (n=60)	t or x^2	*P*
ST-segment depression at 2h after PCI, NO. (%)				
<30%	8(13.33)	3(5.00)	2.50	>0.05
30%-70%	7(11.67)	4(6.67)	0.90	>0.05
>70%	45(75.00)	53(88.33)	3.56	>0.05
TIMI flow, No. (%)				
TIMI flow 0	2(3.33)	4(6.67)	0.18	>0.05
TIMI flow 1	5(8.33)	6(10.00)	0.10	>0.05
TIMI flow 2	8(13.33)	7(11.67)	0.08	>0.05
TIMI flow 3	45(75.00)	43(71.67)	0.17	>0.05
NT-proBNP reduction (pg/ml)	723(304,1506)	719(289,1497)	0.12	>0.05
Bleeding definition, NO. (%)				
Intracerebral hemorrhage	0(0.00)	1(1.67)	-	>0.05
Gastrointestinal bleeding	1(1.67)	6(10.00)	2.43	>0.05
Hemoptysis	0(0.00)	9(15.00)	-	<0.05
BARC 2, NO. (%)	2(3.33)	13(21.67)	9.22	<0.05
Blood transfusion, NO. (%)	0(0.00)	1(1.67)	-	>0.05
BARC, Bleeding Academic Research Consortium; BARC bleeding is graded on a scale of 1 to 5, ranging from minor bleeding that is not actionable (type 1) to fatal bleeding (type 5).				

Table 2: Treatment and procedural characteristics.

the activation of antithrombin and inhibit the activity of thrombin, but it can be caused bleeding when used excessively. Tirofiban attribute to restore blood flow of coronary artery infarction but can increase the risk of bleeding [9]. Bivalirudin, a new direct thrombin inhibitor, is an oligopeptide analogue of hirudin. Bivalirudin has performed more sufficient anticoagulant effect by binding with thrombin directly, specifically and reversibly. Therefore, bivalirudin is especially suitable for the patients who need high intensity anticoagulation therapy in a short term or the ones with high bleeding risk. In our study, bivalirudin or heparin plus tirofiban was administrated as antithrombotic therapy for the 120 elderly patients with acute myocardial infarction undergoing primary PCI, indicating no statistically significant differences between the two groups in the myocardial perfusion level and the improvement of cardiac function (P>0.05), including ST-segment depression at 2 h after intervention, post-PCI TIMI flow grade, the reduction of NT-proBNP serum concentrations of patients on day 7 versus day 1 after PCI. The results indicate that bivalirudin can act as an effective antithrombotic therapy for emergency PCI, which is the same as the past researches [10,11]. Another large-scale clinical study of bivalirudin has found that bivalirudin performs similar anticoagulant effect as heparin, yet it shows the most important advantage for its little bleeding adverse effect as the antithrombotic therapy for PCI, peripheral vascular interventional therapy, heart-lung transplantation and renal dysfunction [12]. The current study also shown that the rate of bleeding in Group A was reduced considerably by bivalirudin compared with that in Group B received heparin plus tirofiban (P<0.05), which was in concordance with the reported researches. There appeared 1 case of gastrointestinal hemorrhage and no cases of intracerebral hemorrhage, hemoptysis in Group A, yet 1 case of intracerebral hemorrhage, 6 cases of gastrointestinal hemorrhage and 9 cases of hemoptysis in Group B. Furthermore, the rate of BARC type 2 bleeding in Group A was lower than that in Group B (P<0.05). These results indicate that bivalirudin can significantly reduce the risk of bleeding compared with heparin plus tirofiban.

In conclusion, this study showed that bivalirudin was effective and safe with lower risks of bleeding compared with heparin plus tirofiban as an anticoagulant therapy for the patients with acute myocardial infarction undergoing emergency PCI. These findings indicated bivalirudin can be used as a routine antithrombotic drug for PCI in clinical.

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