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JNMU

Journal of Nanjing Medical University, 2008, 22(4):238-242

www.elsevier.com/locate/jnmu

Research Paper

Comparison of efficacy and safety of native eptifibatide vs. tirofiban in patients with acute coronary syndrome undergoing percutaneous coronary intervention ☆

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Received 14 April, 2008

Abstract

Objective: To compare clinical outcomes and safety of eptifibatide or tirofiban in patients with acute coronary syndrome(ACS) undergoing percutaneous coronary intervention(PCI). **Methods**:Thirty-six patients with ACS(unstable angina/non-ST-segment elevation myocardial infarction, UA/NSTEMI) who underwent PCI were randomly divided into two groups to receive eptifibatide or tirofiban treatment. Eptifibatide or tirofiban was predominantly initiated in the catheter laboratory before the intervention. In-hospital and 30-day MACE outcomes; bleeding as well as platelet counting were investigated in those two groups. **Results**:No in-hospital and 30-day MACE event occurred in the two groups. The number of ischemia leads after treatment reduced compared to that before PCI in the two groups. There was improvement in the number of ischemia leads for 24 h after administration in the tirofiban group than those in eptifibatide group(4.21 ± 2.46 vs. 3.89 ± 3.31, $P=0.03$). The two groups showed no incidence of massive bleeding. Minor bleeding rates were 16.7% and 22.2% in the two groups respectively. **Conclusion**:Eptifibatide as an adjunct to PCI may further decrease the incidence of ischemia event in patients with ACS and improve the safety, but its long-term efficacy and side effects need further observation.

Key words: acute coronary syndrome; percutaneous coronary intervention; glycoprotein(GP Ⅱb/Ⅲa) antagonist; eptifibatide; tirofiban

INTRODUCTION

Platelet aggregation occurs as a central role of an interconnected pattern of plaque disruption, lipid accumulation, mural thrombus formation, and lesion progression in acute coronary syndrome(ACS). When plaque rupture occurs, the subendothelial protein matrix is disrupted, allowing platelet adhesion molecules such as Von Willebrand factor and collagen to interact with circulating platelets. Platelet activation and degranulation result[1]: In recent years percutaneous coronary intervention(PCI) has become a mainstay for the treatment of coronary artery disease(CAD) especially ACS[2]. However, during and after percutaneous coronary intervention(PCI), disruption of the integrity of the coronary endothelium initiates the thrombus cascade and can cause acute ischemic events[3]. Currently,the glycoprotein Ⅱb/Ⅲa receptor is now recognized as the most specific and potent inhibitors of platelet aggregation. Pharmacological agents directed against this receptor prevent binding of adhesion molecules with potent inhibition of platelet aggregation and reduce clinical morbidity and mortality. The GP Ⅱb/Ⅲa antagonists, eptifibatide and tirofiban, have been evaluated in phase Ⅲ randomized clinical trials and approved for the treatment of patients with ACS who are undergoing PCI in some countries. One of these agents, eptifibatide is a cyclic heptapeptide that mimics the lysine-glycine-aspartic acid sequence originally discovered in the natural GP Ⅱb/Ⅲa inhibitor Barbourin, and it is an intravenous, rapidly reversible, highly specific competitive inhibitor of Glycoprotein(GP) Ⅱb/

☆This work was supported by a grant from ShenZhen Hybio Engineering Co.,Ltd.

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Ⅲa receptors. Tirofiban is a non-peptide which mimics arginine-glutamic-aspartic acid(RGD) sequence to occupy GP Ⅱb/Ⅲa receptor, and it is a competitive inhibitor of formation of fibrinogen or platelet aggregation for Von Willebrand factor. However, there was little data in the pharmacokinetics, pharmacodynamics about the two agents[4-6]. In our country, treatment with tirofiban has been shown to reduce adverse cardiac events when used during PCI over the last decade, while eptifibatide has been observing in clinical trails[7]. The purpose of this study was to compare efficacy and safety between these two agents in patients with ACS undergoing PCI.

MATERIALS AND METHODS

Clinical protocol

This study was a phase Ⅱ, multi-center, randomized, single-blind, positive drug-controlled clinical trial to evaluate the efficacy and safety of native eptifibatide vs. tirofiban as an adjunct to PCI in patients with ACS. The confirmation phase of the trial was conducted at 8 clinical sites in China. Institutional review boards at each facility approved the protocol. Inclusion criteria included age range 18 to 75 years; patients with ACS(unstable angina/non-ST-segment elevation myocardial infarction; according to the 2002 ACC/AHA unstable angina and non-ST-segment elevation myocardial infarction treatment guidelines) who were anticipated to undergo elective or urgent PCI; written informal consent was obtained from all patients before enrollment. Exclusion criteria included ST-segment elevation myocardial infarction (MI); contraindications to treatment or increased risk for bleeding; history of bleeding diathesis or active bleeding within one year; known abnormal blood clotting time or a history of thrombocytopenia; aortic dissection or hemorrhagic stroke; prolonged cardiopulmonary resuscitation, surgery or trauma, active peptic ulcer within 6 weeks; heart, liver, kidney or lung insufficiency; cardiogenic shock; serious valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, arrhythmia; uncontrolled diabetes or other endocrine diseases; serious abnormal laboratory data(Cr > 221 μmol/L; Hb < 110 g/L or platelet count < 90 × 10^9/L; prothrombin time(PT) > 1.2 times control); PCI within the previous 30 days and concurrent treatment with any anticoagulant; a history of stroke or CNS abnormalities; allergy to pork products, aspirin, clopidogrel, eptifibatide, tirofiban, or enoxaparin; uncontrolled hypertension with a systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg; mental diseases, acrasia, innubibus expression; paticipating in other clinical trials within the previous three months; alcoholism, drug addicts and known HIV positive; pregnant women or breast-feeding women.

Study medications were started immediately before PCI. Eptifibatide was administered as a 180 μg/kg bolus with a 18 hour infusion at 2.0 μg/kg/min, with a second 180 μg/kg bolus given 10 minutes after the first. Tirofiban was administered as a 10 μg/kg bolus within 3 minutes and a 36 hour infusion of 0.15 μg/kg/min. All patients received low molecular weight heparin (enoxaparin) at 0.75-1.00 mg/kg subcutaneously before PCI within 8 h. On the day of PCI, all patients received aspirin 300 mg, and 300 mg of clopidogrel if they had not yet received these medicines over three days. Patients receiving drug-eluting stents continued on 75 mg of clopidogrel daily for one year. Aspirin was continued indefinitely. Femoral access sheaths were removed 4 hours after PCI. The use of other anti-angina drugs (beta-blockers, nitrates, calcium antagonists) was permitted at the physician's discretion.

Definition

The key efficacy end point for this analysis was the in-hospital and 30-day of major adverse clinical events (MACE): ① cardiac related death; ② recent myocardial infarction: a typically gradually increased and decreased troponin or the rapid rise and fall of CK-MB with manifestation(s) as followed: a) ischemic symptoms b) ECG displayed a pathological Q wave c) ECG showed ischemia(ST segment upward or downward) d) re-coronary intervention(such as coronary angioplasty), the histopathological findings of acute myocardial necrosis; ③ revascularization(CABG/PCI). Blood samples for troponin T(cTnT), serum creatine kinase MB(CK-MB), prothrombin time(PT), the activated partial thromboplastin time(APTT), and electrocardiographic changes were drawn at baseline(before PCI) and 6, 24, 48 and 72 hours later.

The key safety end points were the incidence of hemorrhage. According to criteria of the Thrombolysis In Myocardial Infarction trial(TIMI), major bleeding was defined as intracranial hemorrhage(confirmed by MRI or computed tomography), bleeding that resulted in a serious or life-threatening clinical event or death, or bleeding accompanied by a decrease in hemoglobin of at least 50 g/L; minor bleeding was defined as clinically serious bleeding(hemoglobin decrease of at least 30 g/L with observed bleeding[including spontaneous gross hematuria or hematemesis] or at least 40 g/L in the absence of observed bleeding) that did not meet the criteria for major bleeding. Other safety end point was the bleeding index, defined as a fall in hemoglobin(g/dl) over the first 24 h, adjusted for whole blood or red blood cell transfusions(pre hemoglobin-post hemoglobin + units transfused). The thrombocytopenia was defined as platelet count >25% decrease or < 90×10^9/L.

Statistical analysis

Patient's data was collected as part of the overall trial. Categorical factors are expressed as percentages and continuous as mean±SD. Differences for the two groups were compared using a Pearson chi-square test for categorical factors and a Wilcoxon rank-sum test for continuous. All analyses were carried out with the SPSS 11.5 system for Windows. A P value of < 0.05 was considered significant.

RESULTS

Baseline characteristics

A total of 36 coronary interventional procedures with ACS were scheduled in our center. Eptifibatide was used in 18 procedures, and tirofiban was used in the other 18 procedures. The characteristics of the patient populations are outlined in Table 1. There were no significant differences in any of the clinical parameters between the two groups($P > 0.05$).

Table 1 Patients' Baseline Characteristics

	eptifibatide (n = 18)	tirofiban (n = 18)	P-value
Age (yrs)	59.7 ± 9.5	55.5 ± 11.2	0.47
Male, n(%)	12(66.7)	16(88.9	0.11
BMI	24.2 ± 2.5	24.4 ± 3.5	0.50
Previous CAD, n(%)	9(50.0)	11(61.1)	0.50
Smoking history, n(%)	6(33.3)	8(44.4)	0.49
Hypertension, n(%)	10(55.6)	9(50.0)	0.74
Diabetes, n(%)	4(22.2)	3(16.7)	0.67
Hyperlipidemia, n(%)	2(11.1)	2(11.1)	1.00
UA, n(%)	16(88.9)	16(88.9)	1.00
NSTEMI, n(%)	2(11.1)	2(11.1)	1.00

CAD=coronary artery disease, UA=unstable angina, NSTEMI=non-ST-segment elevation myocardial infarction.

Clinical outcomes

30-day MACE events did not occur in any patients in-hospital. There was a gradual decline for cTnT and CK-MB in the two groups. cTnT increased in three patients within 24 h after PCI during hospitalization in the two groups, respectively. There was one case with an increase in cTnT above the upper limit of normal in the eptifibatide arm, while two cases in the tirofiban arm(5.6% *vs.* 11.1%, $P > 0.05$). The peak increase from baseline in CK-MB did not differ between the two treatment strategies. No patients showed an increase in CK-MB above the upper limit of normal in the two groups (Table 2). Re-angina occurred in three patients within 30d after administration in the two groups respectively, but laboratory data did not meet myocardial infarction standards.

Static ECG recovery analyses

ST-segment recovery parameters showed no significant differences in the two groups. Ischemia leads reduction displayed a trend toward an improvement with the two therapies at 24h post-PCI compared to ECG of pre-PCI. When patients treated with tirofiban were compared directly, patients who were treated with eptifibatide were associated with a more pronounced ischemia leads reduction(4.21 ± 2.46 for eptifibatide *vs.* 3.89 ± 3.31 for tirofiban, $P = 0.03$)(Table 3).

Table 2 Biomarkers of cTnT, CK-MB during Pre- and Post-PCI

	Eptifibatide (n = 14)	Tirofiban (n = 14)	P-value
Pre-PCI cTnT	0.15 ± 0.29	0.07 ± 0.16	0.09
Post-PCI 6h cTnT	0.05 ± 0.17	0.03 ± 0.08	0.40
Post-PCI 24h cTnT	0.06 ± 0.15	0.02 ± 0.06	0.03*
Post-PCI 48h cTnT	0.03 ± 0.05	0.04 ± 0.09	0.20
Pre-PCI CK-MB	8.12 ± 15.41	10.94 ± 31.17	0.42
Post-PCI 6h CK-MB	4.50 ± 3.62	3.24 ± 3.53	0.61
Post-PCI 24h CK-MB	3.41 ± 3.32	2.89 ± 3.27	0.96
Post-PCI 48h CK-MB	3.87 ± 4.07	1.94 ± 1.84	0.03*

cTnT= troponin T, CK-MB = creatine kinase-myocardial band, PCI = percutaneous coronary intervention.

Table 3 Static ECG Recovery Parameters

	Pre-PCI	Post-PCI 24 h
Eptifibatide	4.22 ± 3.04	4.21 ± 2.46▲
Tirofiban	4.67 ± 3.43	3.89 ± 3.31▲△

▲:There were significant differences in each arm with an ischemia leads reduction event on static ECG at 24 h after PCI compared to that before PCI($P = 0.03$). △:There were significant differences with an ischemia leads reduction event on static ECG at 24 h after PCI between the two arms.

Bleeding complications

There were no significant differences in major bleeding complications. Minor bleeding rates were 16.7% and 22.2% in the two groups respectively which mainly manifested as bleeding gums and skin purpura. Likewise, there was no significant difference in the mean bleeding index, one of the primary end point of the study, between the patients randomized to eptifibatide versus tirofiban, (-3.51 ± 9.70 *vs.* -5.56 ± 14.30; $P > 0.05$). There were no blood transfusions within 24 h in either arm of the study; thus, the bleeding index herein represents the drop in hemoglobin. At most time point, the difference about PT/APTT was not significantly different between the two groups. There were no cases of thrombocytopenia with platelets $< 90 \times 10^9$/L in either arm(Table 4).

DISCUSSION

Plaque rupture and thrombosis are the main causes of ACS. Thrombosis occurs through two interrelated mechanisms:①the adhesion, activation, secretion, and aggregation of platelets; ②amplification of the coagulation cascade, which requires an activated platelet surface for the development of thrombin. Platelet aggregation plays a key role in the pathogenesis of coro-

Table 4 Bleeding Complications

	Eptifibatide (n = 14)	Tirofiban (n = 14)	P-value
TIMI major hemorrhage,n(%)	0	0	NS
TIMI minor hemorrhage,n(%)	3(16.7)	4(22.2)	0.67
bleeding index	-3.51 ± 9.70	0-5.56 ± 14.30	0.56
Pre-PCI PT	13.24 ± 0.98	013.14 ± 0.79	0.90
Post-PCI 6h PT	13.63 ± 1.32	13.84 ± 1.38	0.76
Post-PCI 24h PT	13.34 ± 1.12	13.41 ± 0.82	0.59
Post-PCI 48h PT	13.31 ± 0.83	13.36 ± 1.16	0.28
Pre-PCI APTT	37.18 ± 3.36	37.96 ± 6.53	0.08
Post-PCI 6h APTT	40.21 ± 4.91	44.03 ± 14.45	0.03*
Post-PCI 24h APTT	33.96 ± 5.48	36.56 ± 6.45	0.26
Post-PCI 48h APTT	35.39 ± 7.69	44.20 ± 30.40	0.17
Pre-PCI PLT	188.17 ± 47.84	179.50 ± 42.68	0.58
Post-PCI 6h PLT	196.39 ± 63.69	194.83 ± 49.34	0.26
Post-PCI 24h PLT	189.41 ± 47.88	194.83 ± 60.68	0.84
Post-PCI 48h PLT	184.63 ± 52.00	192.35 ± 53.86	0.89

TIMI=Thrombolysis In Myocardial Infarction, PT= prothrombin time, APTT=the activated partial thromboplastin time.

nary thrombosis, which in turn is responsible for the ischemic complications of percutaneous coronary intervention(PCI)[1]. The integrin GP Ⅱb/Ⅲa receptor on the surface of the platelet, the final common pathway of platelet aggregation, binds circulating macromolecules, which can then cross-link receptors on adjacent platelets, leading to platelet aggregation. Therefore, blockade of GP Ⅱb/Ⅲa receptor interrupts the final common pathway of platelet aggregation. Agents that antagonize the platelet GP Ⅱb/Ⅲa receptor mitigate the thrombosis cascade and as a result offer clinically significant protection against ischemic complications of PCI[4].

Several large randomized clinical trials have clearly indicated that inhibition of platelet aggregation with platelet GP Ⅱb/Ⅲa antagonists improve myocardial ischemia and reduce the rate of myocardial infarction and death in patients with ACS when they were given before the intervention[2,8-9]. ESPRIT trial confirmed that treatment with IV eptifibatide reduced both short-and long-term adverse cardiac events when used during PCI[8]. PRISM-PLUS showed that treatment of tirofiban in ACS patients reduced the rate of death and myocardial infarction within 48 h after treatment, with an absolute reduction of 1.5% to 6.5% in the 30-day risk of death, MI, or urgent revascularization, even with a decline of 20% adverse events in 6 months. Although numerous large-scale clinical studies using GP Ⅱb/Ⅲa inhibitors have been performed in patients undergoing PCI as well as in patients with unstable coronary syndromes, differences in patient populations and trial design do not allow comparisons of different agents. A previous study randomized 30 patients with unstable angina undergoing PCI to receive eptifibatide, abciximab, or tirofiban to assess the degree of platelet aggregation inhibition at numerous time points until hospital discharge. Eptifibatide-treated patients had greatest inhibition of platelet aggregation at the end of the infusion and the degree of platelet inhibition was least with tirofiban. The numbers in this study were too small to assess clinical differences[9]. In 2002, the COMPARE trial provided a direct pharmacodynamic comparison of conventional doses of abciximab, eptifibatide, and tirofiban based upon previous study. It demonstrated that tirofiban inhibited platelet activity to a lower degree than with eptifibatide and abciximab[10]. The study did not evaluate the pharmacodynamics of currently used doses of eptifibatide(ESPRIT trial) or tirofiban(ADVANCE trial), although it would be expected that these more potent doses would provide greater degree of platelet inhibition[8,11]. Danzi *et al.* compared these 2-molecule agents in their newly prescribed doses(eptifibatide 180 μg/kg double bolus followed by 2 μg/[kg min] for 24 hours according to the ESPRIT dosing regimen and tirofiban 25 μg/kg bolus followed by an infusion 0.15 μg/[kg min] for 18 hours as recommended in ADVANCE trial). This study concluded that high-dose tirofiban was a more effective drug in rapidly achieving optimal platelet inhibition after PCI[12]. More recently, the MR PCI study demonstrates that high-dose tirofiban in patients undergoing high-risk elective PCI is associated with greater IPA at 10 min-utes and at 6 to 8 hours as compared with double-bolus eptifibatide[13]. In our study we found all patients did not suffer any in-hospital and 30-day MACE event. In addition, resolution of ST-segment is a simple, non-invasive biomarker that correlates with recanalization of the epicardial infarctrelated artery, successful restoration of myocardial tissue perfusion, and a lower risk of mortality[14]. We discovered that ischemia leads reduction displayed a trend toward an improvement with the two therapies at 24h post-PCI compared to ECG of pre-PCI. Patients treated with tirofiban compared directly to patients who were treated with eptifibatide were associated with a higher ischemia leads reduction. This may be caused by the samples of the study as well as the different pharmacology mechanisms of the two agents.

The use of any of the commercially available GP Ⅱb/Ⅲa antagonists was associated with a low incidence of bleeding, even in patients who underwent PCI. PRISM-PLUS trial showed major bleeding rate is 1.4% in the tirofiban group, while 0.8% in the placebo group (P > 0.05). PURSUIT trial displayed the incidence of bleeding complication was 10.6% in the eptifibatide group, while 9.1% in the placebo group(P > 0.05)[15]. There were no significant differences in massive bleeding, minor bleeding as well as bleeding index

between the two groups in our study. Thrombocytopenia is uncommon, but the complication can increase the bleeding risk. Our study showed no thrombocytopenia in both groups.

The sample size was not powered to assess differences in clinical outcome. Because there were no adverse events reported beyond hospitalization during the 30-day follow-up, we could not establish any significant association between the treatment regimens and clinical efficacy outcomes. Secondly, a more potent approach should be utilized to observe differences of different agents, e.g. the inhibition of platelet aggregation(IPA). Finally, further observation is required to evaluate the long-term efficacy and side effects between the two agents.

When GP Ⅱb/Ⅲa receptor antagonists were used as adjunctive therapy to aspirin, heparin and other oral anti-platelet agents in PCI, comparable good rates of clinical endpoints, and low rates of bleeding complications were attained. Patients with ACS undergoing PCI treated with eptifibatide may further decrease the incidence of ischemia event with low bleeding complications, but its long-term efficacy and side effects need further observation.

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