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Original article

Safety and efficacy of Bivalirudin with Glycoprotein IIb/IIIa for high-risk percutaneous coronary intervention

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ARTICLE INFO

Article history:

Received 24 April 2012

Received in revised form

18 June 2012

Accepted 17 July 2012

Available online 27 July 2012

Keywords:

Bivalirudin

Glycoprotein IIb/IIIa inhibitor

PCI

Safety

ABSTRACT

Aims: The aim of the study was to assess the safety and efficacy of Bivalirudin + Glycoprotein (Gp) IIb/IIIa inhibitor as compared to unfractionated Heparin (UFH) + Gp IIb/IIIa inhibitor in high risk patients undergoing elective percutaneous coronary intervention (PCI). The primary end point was time to sheath removal and ambulation where as peri-procedure myocardial damage, access site bleeding and major adverse cardiac events (MACE) rates were secondary end points.

Methods: One hundred and one high risk patients undergoing elective PCI were randomly assigned to either Bivalirudin + GpIIb/IIIa inhibitor or UFH + Gp IIb/IIIa inhibitor. PCI was performed by standard technique and activated clotting time was monitored immediately on arrival to recovery area and every 60 min thereafter. Sheath were pulled out once ACT was below 150 seconds and patients were mobilized 6hrs after sheath were removed. Peri-procedure myocardial damage was assessed by serial Trop I levels.

Results: Patient assigned to Bivalirudin + Tirofiban has significantly reduced time to sheath removal and ambulation as compared to those who received UFH + tirofiban ($p < 0.0001$) although peak Act did not differ in the groups. Peak Trop I levels were significantly lower in Bivalirudin + Tirofiban group ($p = 0.023$) and peri-procedure Trop I elevation occurred in significantly lower number of patients treated with Bivalirudin + Tirofiban ($p = 0.029$).

Conclusions: The combination of Bivalirudin + Tirofiban was safe and effective as compared to UFH + Tirofiban in high risk patients undergoing elective PCI.

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1. Introduction

Percutaneous coronary intervention (PCI) is a commonly performed procedure in patients with coronary artery disease. The American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines

recommend initiation of antiplatelet therapy (aspirin and clopidogrel), antithrombotic therapy and Glycoprotein (GP) IIb/IIIa inhibitors for Non ST elevation acute coronary syndrome patients undergoing PCI. Although this intensive antiplatelet and antithrombin regimen reduces ischemic events, such treatment regimens are associated with an

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<http://dx.doi.org/10.1016/j.ihj.2012.07.022>

increased risk of bleeding, and need for prolonged bed rest.¹ The direct thrombin inhibitor bivalirudin has rapid onset of action, predictable response and possible inhibition of platelet aggregation.²

The recent research on antithrombotics in PCI has focused on finding a balance between ischemic complications such as peri-procedural myocardial infarction (MI), stent thrombosis and catheter thrombosis vs. bleeding events such as major and minor bleeding, vascular access site bleeding and need for blood transfusion.

The Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial had shown that treatment with bivalirudin monotherapy was associated with similar rates of composite ischemia but significantly reduced bleeding at 30 days and similar rates of mortality and composite ischemia at 1 year compared with unfractionated heparin (UFH) or enoxaparin + a GP IIb/IIIa inhibitor.³ Moreover studies have shown that patients who received bivalirudin needed significantly less time for the activated clotting time to normalize.⁴ Studies have further established the important relationship between iatrogenic bleeding complications and subsequent mortality in patients with Acute Coronary Syndrome.¹

A number of trials, the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial, the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial and the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZON AMI) trial had compared bivalirudin alone with UFH + GP IIb/IIIa inhibitor.^{1,5,6} However, clinicians in India use GP IIb/IIIa inhibitor in the majority of PCI procedures and almost all patients undergoing high-risk PCI receive a GP IIb/IIIa inhibitor. So in our study, we wanted to assess the safety and efficacy of bivalirudin + GP IIb/IIIa inhibitor as compared to UFH with GP IIb/IIIa inhibitor on time to sheath removal, ambulation time and peri-procedural adverse event rates.

2. Methods

2.1. Study population

We enrolled patients for the study from a single centre from February 2010 through May 2010 with the inclusion criteria of age >18 years and ≤75 years undergoing elective high risk PCI as defined by patients on chronic antiplatelet therapy with aspirin, clopidogrel for >5 days or received total dose of >300 mg for more than 24 h and had severe coronary artery disease amenable to PCI. High risk criteria required the presence of at least one clinical criterion of: prior stroke, prior peripheral vascular disease, diabetes, documented microalbuminuria, prior MI, unstable angina, ECG changes of ST depression of 1 mm or elevated cardiac enzymes consistent with Non ST elevation MI. The exclusion criteria were acute ST-segment elevation MI or shock; bleeding diathesis or major bleeding within 2 weeks; thrombocytopenia; creatinine clearance ≤30 ml/min; recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin or low molecular weight heparin within 8 h. The study was approved by Institutional Ethical Committee and all patients gave written informed consent.

2.2. Study protocol

One hundred and one patients were randomly assigned, in an open-label fashion to treatment with UFH + a GP IIb/IIIa inhibitor or bivalirudin + a GP IIb/IIIa inhibitor. UFH was administered as an intravenous bolus of 70 IU/kg of body weight and if required a subsequent bolus of 20 IU/kg targeted to an activated clotting time of 200–250 s. Bivalirudin was administered as an intravenous bolus of 0.75 mg per kg of body weight followed by infusion of 1.75 mg per kg per hour. If UFH was administered in a patient in the bivalirudin group, bivalirudin was started 30 min later but in all cases before PCI. Both antithrombotic agents were discontinued, as specified by the protocol, at the completion of PCI but were continued at low doses if they were clinically indicated. Tirofiban was the GP IIb/IIIa inhibitor used and was administered to patients of both groups as a 25 mcg/kg bolus followed by an infusion of 0.15 mcg/kg/min for a period of 4 h after the procedure.

Activated clotting time was measured immediately on the patient's arrival to recovery and then every 60 min. Serial activated clotting time was measured until the desired threshold for sheath pull was achieved. The desired activated clotting time for sheath pull was below 150 ms. Coronary stenting with either bare-metal or drug-eluting stent were performed according to the choice of the physician. Sheaths were removed and manual compression was applied as soon as the activated clotting time fell below 150 ms. The peri-procedural myocardial damage was assessed using the baseline and at discharge hours' troponin levels.

The patients were mobilized after 6 h of sheath removal and were typically discharged from the hospital 24–48 h after the procedure. All patients were followed up for a period of 30 days for major adverse cardiac events including death, MI, target-vessel revascularization for ischemia, and stroke.

2.3. Study endpoints

The primary endpoint of the study was post procedural time to sheath removal and ambulation of the patient. The secondary endpoints were post procedure access site bleeding rates, peri-procedural myocardial damage assessed by rise in Troponin I and adverse clinical events, defined as the combination of major bleeding and/or major adverse cardiovascular events (MACE), including death, MI, target-vessel revascularization for ischemia, and stroke within 30 days. The definition of major bleeding was based on the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial: and included intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g per decilitre any decrease in hemoglobin of more than 4 g per deciliter; or transfusion of 2 or more units of packed red cells or whole blood.⁵ Peri-procedural myocardial damage was defined as a typical rise of Troponin I more than 3 times the upper limit of normal. Recurrent MI was defined in the presence of both ischemic pain and new >50% increase in Troponin I level. The MI definitions were adapted from the Joint European Society of Cardiology/American College of Cardiology Committee statement on universal definition of MI.⁷ Death from cardiac causes was defined as death due to acute MI, cardiac perforation or pericardial tamponade,

arrhythmia or conduction abnormality, stroke, procedural complications, or any death for which a cardiac cause could not be ruled out. Death from non cardiac causes included bleeding-related death. Stent thrombosis was defined as the definite or probable occurrence of a stent-related thrombosis event according to the Academic Research Consortium classification.⁸

2.4. Statistical analysis

Categorical outcomes were compared by means of Fisher's exact test. Continuous variables were compared by means of the student t-test. $p < 0.05$ was used to test for significance.

3. Results

Between February 5, 2010 and May 5, 2010, a total of 101 patients who met the inclusion criteria and were undergoing elective high risk PCI were randomly assigned to treatment with UFH + tirofiban (52 patients) or with bivalirudin + tirofiban (49 patients). Details of study medication administration were as per the study protocol. All patients received the randomly assigned drug.

Patient disposition is presented in Table 1. The mean age was 56 years and 87% of the patients were men. In our study 19 (36.54%) patients of heparin group A and 13 (26.53%) patients had raised baseline Troponin I level (p value = 0.29) indicating ongoing ischemia. Procedural Characteristics are shown in Table 2. The average number of lesions treated per patient was 1.56 ± 0.67 in UHF + tirofiban group and 1.47 ± 0.62 in bivalirudin + tirofiban group ($p = 0.49$).

Table 3 shows the clinical outcomes of the study drug on sheath removal time, peri-procedural myocardial damage rates

and major adverse cardiac events. Patients who were assigned to receive bivalirudin with tirofiban, as compared with those who were assigned to receive UFH + tirofiban, had a significantly reduced time to sheath removal and ambulation ($p < 0.0001$). The peak ACT did not differ significantly in the groups ($p = 0.28$).

There was a significant difference in the peak Troponin I levels in the bivalirudin + GP IIb/IIIa inhibitor as compared to the UFH + GP IIb/IIIa inhibitor group (0.058 ± 0.717 vs. 0.422 ± 0.854 , $p = 0.023$). The rate of peri-procedural rise in Troponin I was 49.89% in the bivalirudin + tirofiban group as compared to 63.46% in the UFH + tirofiban ($p = 0.029$). Ejection fraction; procedural duration; number of vessel treated; frequency of de novo, calcified lesions and stent types did not differ between the patients of the two groups (Table 2).

Among the 101 patients in whom stents were successfully implanted, in the bivalirudin group one patient had minor oral bleeding and one patient had thrombocytopenia. In the heparin group, one patient had hypotension requiring inotropic support. There were no 30-day MACE events including death, MI, target-vessel revascularization for ischemia, and stroke or 30 days stent thrombosis event.

4. Discussion

The study represents a contemporary evaluation of the direct thrombin inhibitor bivalirudin with GP IIb/IIIa inhibitor tirofiban on time to ambulation; peri-procedural myocardial damage rates and 30 days MACE including death, myocardial infarction, target-vessel revascularization for ischemia, and stroke. The study demonstrates that patients treated with bivalirudin + GP IIb/IIIa inhibitor had similar safety as UFH + GP IIb/IIIa inhibitor with higher efficacy in reducing

Table 1 – Patient demographics.

Variable	Unfractionated Heparin + Tirofiban (n = 52)	Bivalirudin + Tirofiban (n = 49)	p value
Age (years)	56.577 $\pm$ 10.044	55.26 $\pm$ 10.412	0.52
Men	44 (84.6)	44 (89.8)	0.55
Hypertension	39 (75)	38 (77.6)	0.818
Current smoker	11 (21.2)	8 (16.3)	0.615
Hyperlipidemia	3 (5.8)	9 (18.4)	0.067
Diabetes	22 (42.3)	18 (36.7)	0.68
Angina			
Unstable	23 (43.2)	21 (42.9)	1.00
Stable	11 (21.2)	16 (32.7)	0.26
History of myocardial infarction	18 (34.6)	12 (24.5)	0.29
Number of diseased coronary vessels			
Single vessel disease	20 (38.5)	25 (51)	0.23
Double vessel disease	22 (42.3)	20 (40.8)	1.0
Triple vessel disease	10 (19.2)	4 (8.5)	0.151
History of coronary bypass surgery	1 (1.9)	0	1.0
History of prior angioplasty	6 (11.5)	2 (4.1)	0.27
Body weight (kg)	69.2 $\pm$ 10.96	68.08 $\pm$ 9.56	0.58
Body mass index (kg/m ²)	24.14 $\pm$ 2.62	23.78 $\pm$ 2.86	0.51
Serum creatinine (mg/dl)	0.97 $\pm$ 0.28	0.93 $\pm$ 0.26	0.41
Ejection fraction (%)	46.96 $\pm$ 14.34	50.94 $\pm$ 11.89	0.13
Increased baseline troponin I (μ g/L)	19 (36.54)	13 (26.53)	0.29

Data are expressed as mean $\pm$ SD or number of patient (percentage).

Table 2 – Angiographic and procedural characteristics.

Variable	Unfractionated Heparin + Tirofiban (n = 52)	Bivalirudin + Tirofiban (n = 49)	p value
Number of Lesions treated	82	71	
Procedure duration (min)	38.04 ± 16.65	34.78 ± 12.11	0.27
Average number of lesions treated per patients	1.56 ± 0.67	1.47 ± 0.62	0.49
Target vessel location			
Left main	1 (1.22)	0	1.0
Left anterior descending	38 (46.34)	35 (49.30)	0.75
Left circumflex artery	19 (23.17)	19 (26.76)	0.71
Right coronary artery	24 (29.27)	17 (34.69)	0.47
Complex B2/C	81 (98.78)	70 (98.59)	1.0
Type of Intervention			
Placement of drug eluting stent	51 (62.19)	41 (83.67)	0.62
Placement of bare metal stent	30 (36.58)	30 (42.25)	0.51
Balloon angioplasty	1 (1.22)	0	1.0
Peak activated clotting time (seconds)	264.2 ± 39.12	286.4 ± 43.63	0.28
Peak troponin I (μg/L)	0.42 ± 0.85	0.06 ± 0.72	0.02
Data are expressed as mean ± SD or as number (percentage).			

peri-procedural myocardial damage rates and quicker ambulation rates. Reports from a subgroup analysis of patients in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial who received bivalirudin and provisional GP IIb/IIIa inhibitor demonstrated that a strategy of bivalirudin with provisional GP IIb/IIIa inhibition was non inferior to heparin with planned GP IIb/IIIa inhibition with respect to suppression of 30-day ischemic endpoints.⁹ By 30 days, the composite endpoint of death, MI, or urgent repeat revascularization occurred in 7.6% of patients receiving bivalirudin as compared to 7.1% of patients in the heparin plus planned GP IIb/IIIa inhibitor group ($p = 0.40$) with no difference in 1 year mortality (1.9% vs. 2.5% respectively, $p = 0.16$).^{5,10} The incidence of short term ischemic and hemorrhagic complications was higher in the patients receiving provisional GP IIb/IIIa inhibitor compared to those who did not require it. Exaire et al suggested that inferior outcomes in patients requiring provisional GP IIb/IIIa inhibition in addition to bivalirudin was due to the fact that the GP IIb/IIIa inhibitor was administered as a bailout once patients developed procedural complications rather than from a deleterious effect of the GP IIb/IIIa inhibitor per se given during PCI.

A study by Feldman et al suggested that the addition of provisional GP IIb/IIIa inhibition to bivalirudin treated patients developing angiographic procedural complications as compared to bivalirudin alone results in an increase in

hemorrhagic events, but may neutralize the negative impact of the peri-procedural ischemia.¹¹

Our study data showed that the peri-procedural myocardial damage was significantly lower in the bivalirudin + GP IIb/IIIa inhibitor as compared to UFH + GP IIb/IIIa inhibitor ($p < 0.023$). A large scale, prospective randomized trial involving patients with moderate or high risk acute coronary syndrome undergoing early invasive strategy, showed that the use of bivalirudin alone with provisional use of a GP IIb/IIIa inhibitor was associated with ischemic complications that were no inferior to those associated with the use of heparin (either unfractionated heparin or enoxaparin) plus a GP IIb/IIIa inhibitor with significantly lower bleeding rates in the bivalirudin monotherapy group.¹² A subsequent study, the Harmonizing Outcomes with Revascularization and stents in Acute Myocardial Infarction (HORIZON-AMI) compared bivalirudin monotherapy with combination UFH + GP IIb/IIIa inhibitor treatment in patients with ST elevation MI undergoing PCI. The primary outcome of composite ischemia rates were similar between treatment groups, however, the incidence of acute stent thrombosis was significantly higher in the bivalirudin group. (1.3% vs. 0.3%; $p < 0.01$).⁶

The peri-procedural myocardial damage is assessed by the post PCI rise in cardiac enzyme levels. The studies using CK-MB as marker of myocardial damage have observed the incidence of 5–30% depending upon the subgroup of patients

Table 3 – Clinical outcomes.

Observation	Unfractionated heparin + tirofiban (n = 52)	Bivalirudin + tirofiban (n = 49)	p value
Peri-procedural myocardial damage	33 (63.46)	20 (49.89)	0.03
Sheath removal time (h)	3.82 ± 0.95	2.31 ± 0.59	0.0001
Ambulation time (h)	9.89 ± 1.06	8.23 ± 0.69	0.0001
Adverse clinical event at 30 days ^a	0	0	1.00

Data are expressed as mean ± SD or as number of patients (percentage).

a Defined as the combination of major bleeding and/or major adverse cardiovascular events (MACE), including death, myocardial infarction, target-vessel revascularization for ischemia, and stroke within 30 days.

undergoing the intervention.¹³ When Troponin is used for assessment of myocardial damage, the incidence of myocardial damage may go up to almost 50%.^{14,15} This is because of increased sensitivity of serum Troponin levels to detect the myocardial damage. Similar findings have been reported by ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty)¹⁶ study. The incidence of post procedure rise in CK-MB level was seen 14% in patients of 600 mg and 26% in patients of 300 mg loading dose group ($P = 0.036$). But in similar patients, the post procedure rise in Troponin I was seen in 26% in patients of 600 mg and 44% patients of 300 mg loading dose indicating the high sensitivity of Troponin I to detect the myocardial damage. In our study the rate of peri-procedural myocardial damage is similar to that of ARMYDA-2 trial which can be explained on the basis of increased sensitivity of Serum Troponin I for the assessment of myocardial damage.

In the current study the patient population in bivalirudin + GP IIb/IIIa inhibitor group spent markedly lesser time in the recovery area due to less time required to sheath removal and ambulation ($p < 0.0001$). This result is consistent with the study by Schussler et al which demonstrated that bivalirudin significantly reduces the duration of stay in the recovery area for post PCI patients.

5. Conclusion

Bivalirudin + Glycoprotein IIb/IIIa inhibitor appears to be a safe and effective adjuvant pharmacological treatment during high risk PCI. The main benefit being reduction in the time spent in the recovery area which would theoretically lead to a reduction of cost, valuable resources and reduced load on the recovery staff.⁴ The lower peri-procedural myocardial damage rates associated with PCI in the Bivalirudin group would improve outcomes in patients undergoing high risk PCI. Bivalirudin appears to be the preferred antithrombotic in high risk patients undergoing PCI.¹⁷

Conflicts of interest

All authors have none to declare.

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