Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Bivalirudin plus loading dose of cilostazol-based triple-antiplatelet in treatment of non-ST-elevation myocardial infarction following percutaneous coronary intervention

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
28 September 2015
Number of times this article has been viewed

Mei Wang
Guoru Zhang
Yaling Wang
Kun Zhou
Tao Liu
Yang Zhang
Anjun Guo
Yu An
Xiaodan Zhang
Yongjun Li

Department of Cardiology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China

Objective: To study the effect of bivalirudin plus loading dose of cilostazol-based triple-antiplatelet therapy strategy in patients undergoing percutaneous coronary intervention (PCI).

Methods: One hundred and fifty-three patients with non-ST-segment elevation myocardial infarction who underwent PCI were divided into control group and cilostazol group. Patients in control group were given aspirin and clopidogrel and those in cilostazol group were given aspirin, clopidogrel, and cilostazol once 2 hours before PCI and for 30 days after PCI. Bivalirudin was given to all patients before and during the PCI.

Results: After PCI, the Thrombolysis In Myocardial Infarction myocardial perfusion grade (TMPG) III in cilostazol group was higher than that in control group (89.19% versus 72.15%, $P<0.05$). At 30 days, the incidence of major adverse cardiac events was significantly lower in cilostazol group compared with that in control group (6.76% versus 17.72%, $P<0.05$). However, the rates of cardiac death, nonfatal reinfarction, target vessel revascularization, new congestive heart failure, and subacute stent thrombosis did not significantly differ between the two groups. In addition, the rates of minor or major bleeding or thrombocytopenia did not significantly differ between the two groups.

Conclusion: Bivalirudin plus loading dose of cilostazol-based triple-antiplatelet therapy strategy in PCI increased TMPG III, decreased major adverse cardiac events, and did not increase the incidence of bleeding and thrombocytopenia.

Keywords: triple-antiplatelet therapy, bivalirudin, percutaneous coronary intervention

Introduction

To reduce the incidence of thrombotic and bleeding complications during and following percutaneous coronary intervention (PCI), many different antithrombotic regimens have been investigated. Compared with the combination of heparin and glycoprotein IIb/IIIa inhibitors, the direct thrombin inhibitor bivalirudin significantly reduced the incidence of major bleeding after 30 days in patients with ST-segment elevation myocardial infarction undergoing primary PCI in a HORIZONS-AMI trial, but the risk of acute stent thrombosis increased within 24 hours.[1] The early elevation in stent thrombosis with bivalirudin alone probably results from platelet activation induced by adenosine diphosphate before maximal thienopyridine blockade of the $P2Y_{12}$ receptor or by the activity of residual thrombin following the discontinuation of bivalirudin. Cilostazol, as a selective and reversible phosphodiesterase type III inhibitor, exerts a unique vasodilatory and antithrombotic effect, according to a new mechanism.[2,3] After PCI, triple-antiplatelet

Correspondence: Yongjun Li
Department of Cardiology,
The Second Hospital of Hebei Medical University, Shijiazhuang, 215 Hepingxi Road, Shijiazhuang, Hebei 050000, People's Republic of China
Tel +86 311 6600 2126
Fax +86 311 6600 2126
Email liyongjun@fexmail.cn

therapy (aspirin, clopidogrel, and cilostazol) has been proven to be correlated with a decreased incidence of stent thrombosis and major adverse cardiac events (MACE) compared with standard dual-antiplatelet therapy in certain clinical investigations.[4,5] However, the effect of loading dose of cilostazol before PCI plus bivalirudin strategy in PCI procedure is largely elusive. This study is designed to evaluate the effects of loading dose of cilostazol-based triple-antiplatelet therapy plus bivalirudin strategy in patients with non-ST-segment elevation myocardial infarction treated with PCI.

Methods

Study patients

The patients who were diagnosed with non-ST-segment elevation myocardial infarction and underwent PCI were enrolled. Inclusion criteria were: 1) aged between 20 and 80 years; 2) accelerated or prolonged angina enduring over 20 minutes or recurrent episodes of angina at rest or during minimal exertion within the preceding 48 hours; 3) cardiac biomarker (creatine kinase MB or troponin) levels exceeding the upper limit of the normal range; 4) coronary stenoses which should be treated with PCI; and 5) undergoing PCI with drug-eluting stent implantation. Exclusion criteria were: 1) acute ST-segment elevation myocardial infarction or shock; 2) known bleeding disorders or liver disease; 3) thrombocytopenia; 4) calculated creatinine clearance level of $<$30 mL/min; 5) current warfarin use; 6) use of glycoprotein IIb/IIIa inhibitor, abciximab, or fibrinolytic; and 7) allergy to selected drugs or iodinated contrast which could not be premedicated. This study protocol was approved by the ethics committees of our hospital (The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China). Written informed consent was obtained from all of the patients.

Randomization and antiplatelet therapy

Patients were randomly divided into triple-antiplatelet group (cilostazol group) and dual-antiplatelet group (control group) according to a computer-generated randomization list. At least 2 hours before PCI, patients in the cilostazol group were given with 300 mg of aspirin (Bayer AG, Leverkusen, Germany), 600 mg of clopidogrel (Sanofi SA, Paris, France), and 200 mg of cilostazol (Otsuka Pharmaceutical Co, Zhejiang, People's Republic of China), followed by aspirin 100 mg/day, clopidogrel 75 mg/day, and cilostazol 100 mg twice daily for 30 days. Those in the control group were given 600 mg of clopidogrel and 300 mg of aspirin, followed by aspirin 100 mg/day and clopidogrel 75 mg/day for 30 days.

Procedures of stent implantation

A dosage of 3,000 U of heparin was administered via intravenous route prior to coronary angiography. After the decision to conduct PCI, all patients received a dose of 0.75 mg of bivalirudin/kg (Litai pharmaceutical co., Ltd, Shenzhen, People's Republic of China) followed by an infusion of 1.75 mg/kg/hour throughout the procedure. The activated clotting time was not monitored intraoperatively. Then, strictly according to the standard procedures, balloon predilatation and stent implantation were conducted.

Evaluation of therapeutic efficacy

Thrombolysis In Myocardial Infarction (TIMI) flow grade[6] and TIMI myocardial perfusion grade (TMPG)[7] were utilized to evaluate the culprit vessel flow and myocardial tissue-level perfusion. TMPG was evaluated merely in the region provided by the culprit vessel. Standard 2-dimensional echocardiography was used to evaluate left ventricular ejection fraction before and at 30 days after PCI. MACE, such as cardiac death, nonfatal reinfarction, target vessel revascularization, new congestive heart failure, or subacute stent thrombosis were also assessed at 30 days after PCI. Major bleeding was defined as a decrease in hemoglobin $\geq$2.0 mmol/L and the requirement for transfusion of $\geq$2 units of blood, or as retroperitoneal, intracranial, or gastrointestinal bleeding. Minor bleeding was defined as a decline in hemoglobin $<$2.0 mmol/L without the requirement to perform blood transfusion.[8]

Statistical analysis

Continuous data were expressed as $\bar{x} \pm$ standard deviation (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

Clinical and angiographic data at baseline

Enrollment of 153 patients was completed between October 2010 and August 2012. The baseline clinical and angiographic data of the patients are illustrated in Table 1. No significant differences were found in baseline characteristics between the two groups.

Coronary angiography results

No obvious difference was noted in the characteristics of the culprit vessels or the use of drug-eluting stents between two groups (Table 2). Prior to PCI, the mean TIMI flow grade and TMPG were almost equivalent between the two groups.

Table 1 Baseline characteristics of the patients

	Control group (n=79)	Cilostazol group (n=74)	*P*-value
Age (years)	63.71±8.64	61.03±8.33	>0.05
Male	62 (78.48)	58 (78.38)	>0.05
Smoking	38 (48.10)	35 (47.30)	>0.05
Prior MI	9 (11.39)	8 (10.81)	>0.05
Prior CABG	3 (3.80)	3 (4.05)	>0.05
Hypertension	48 (60.76)	46 (62.16)	>0.05
Diabetes	23 (29.11)	20 (27.03)	>0.05
Hyperlipidemia	37 (46.84)	35 (47.30)	>0.05

Note: Data given as number (%) or mean ± standard deviation.
Abbreviations: CABG, coronary artery bypass grafting; MI, myocardial infarction.

Following PCI, the TMPG III in the cilostazol group was significantly higher than that in the control group, as shown in Table 3 ($P<0.05$).

Clinical results

As demonstrated in Table 4, the left ventricular ejection fraction did not significantly differ between the two groups before and at 30 days after PCI (both $P<0.05$). The MACE rate in the cilostazol group was significantly lower than that in the control group at 30 days after PCI ($P<0.05$). However, the rates of cardiac death, nonfatal reinfarction, target vessel revascularization, new congestive heart failure, and subacute stent thrombosis did not significantly differ between two groups.

Thrombocytopenia and bleeding complications

The rates of minor or major bleeding or thrombocytopenia did not significantly differ between the two groups (Table 4, $P>0.05$).

Table 2 Angiographic findings

Index	Control group (n=79)	Cilostazol group (n=74)	*P*-value
Target vessel			
LAD	42 (53.16)	39 (52.70)	>0.05
LCX	23 (29.11)	21 (28.38)	>0.05
RCA	12 (15.19)	11 (14.86)	>0.05
LM	2 (2.53)	3 (4.05)	>0.05
Lesion type			
A	18 (22.78)	16 (21.62)	>0.05
B	45 (58.23)	44 (59.46)	>0.05
C	16 (20.25)	14 (18.92)	>0.05
Number of stents	1.36±0.56	1.37±0.58	>0.05
Stent diameter	3.17±0.48	3.16±0.48	>0.05
Stent length	23.92±7.13	23.84±7.05	>0.05

Note: Data given as number (%) or mean ± standard deviation.
Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main stem; RCA, right coronary artery.

Table 3 TIMI flow grade and TMPG during PCI

	Control group (n=79)	Cilostazol group (n=74)	*P*-value
TIMI flow grade before PCI			
0	3 (3.80)	6 (8.11)	>0.05
I	10 (12.66)	8 (10.82)	>0.05
II	12 (15.19)	9 (12.16)	>0.05
III	54 (68.35)	51 (68.92)	>0.05
TIMI flow grade after PCI			
0	0	0	>0.05
I	2 (2.53)	1 (1.35)	>0.05
II	1 (1.27)	1 (1.35)	>0.05
III	76 (96.20)	72 (97.30)	>0.05
TMPG before PCI			
0	6 (7.59)	8 (10.81)	>0.05
I	12 (15.19)	9 (12.16)	>0.05
II	8 (10.13)	15 (20.27)	>0.05
III	53 (67.09)	42 (56.76)	>0.05
TMPG after PCI			
0	2 (2.53)	1 (1.35)	>0.05
I	8 (10.13)	1 (1.35)	<0.05
II	12 (15.19)	6 (8.11)	>0.05
III	57 (72.15)	66 (89.19)	<0.05

Note: Data given as number (%).
Abbreviations: PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; TMPG, TIMI myocardial perfusion grade.

Discussion

Previous studies of antithrombotic strategy in patient who underwent PCI focused mostly on bivalirudin or triple-antiplatelet therapy after PCI. The ISAR-REACT 3 trial had shown that although bivalirudin failed to offer a net clinical benefit as compared with unfractionated heparin, it significantly decreased the incidence of major bleeding for patients with stable/unstable angina undergoing PCI after

Table 4 The 30-day MACE and complications after PCI

Index	Control group (n=79)	Cilostazol group (n=74)	*P*-value
LVEF (%)			
Before PCI	50.12±4.78	50.16±4.63	>0.05
30 days after PCI	52.73±5.58	52.80±5.35	>0.05
MACE	14 (17.72)	5 (6.76)	<0.05
Cardiac death	2 (2.53)	1 (1.35)	>0.05
Nonfatal reinfarction	4 (5.06)	1 (1.35)	>0.05
TVR	5 (6.33)	2 (2.70)	>0.05
New congestive heart failure	3 (3.80)	1 (1.35)	>0.05
Subacute stent thrombosis	2 (2.53)	0 (0)	>0.05
Bleeding (TIMI classification)			
Minor bleeding	2 (2.53)	3 (4.05)	>0.05
Major bleeding	1 (1.27)	1 (1.35)	>0.05
Thrombocytopenia	1 (1.27)	1 (1.35)	>0.05

Note: Data given as number (%) or mean ± standard deviation.
Abbreviations: LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; TVR, target vessel revascularization.

pretreatment with clopidogrel.[9] In the ACUITY trial, patients with a moderate or high risk of acute coronary syndromes and receiving invasive therapy using glycoprotein IIb/IIIa inhibitors were enrolled, and it was demonstrated that bivalirudin was correlated with the incidence of bleeding and ischemia resembling those treated with heparin.[10] In the HORIZONS-AMI trial,[1] the risk of acute stent thrombosis was increased within 24 hours in patients who were diagnosed with ST-segment elevation myocardial infarction and underwent PCI. The early elevation in stent thrombosis with bivalirudin alone possibly results from platelet activation caused by adenosine diphosphate prior to maximal thienopyridine blockade of the $P2Y_{12}$ receptor or by the activity of residual thrombin following the suspended use of bivalirudin. Adequate platelet inhibition probably leads to the reduced risk of ischemic clinical events.

Cilostazol is a potent type III phosphodiesterase inhibitor which was already well-known for its various benefits, such as antiplatelet and antithrombotic effects, vasodilating properties, reductions in clopidogrel resistance, and other pleiotropic actions.[11–13] Cilostazol has been proven to suppress ADP-induced platelet aggregation, collagen, arachidonic acid, and epinephrine.[14] Based on the studies above, combined administration of cilostazol, clopidogrel, and aspirin known as triple-antiplatelet therapy had been recommended. A previous study demonstrated that the incidences of death, myocardial infarction, target lesion revascularization, or stent thrombosis after stenting were reduced by approximately 50% using triple-antiplatelet therapy compared with those by dual-antiplatelet therapy.[15] Recent clinical trials found that triple-antiplatelet therapy exerts a more potent inhibition upon ADP-induced platelet aggregation compared with dual-antiplatelet therapy.[16,17] Previous studies demonstrated that triple-antiplatelet therapy decreased the risk of long-term cardiac and cerebral events after PCI for patients with acute coronary syndromes, especially those with high-risk profiles.[18] But a trial involving 120 patients with stable angina demonstrated that adjunctive cilostazol pretreatment might not significantly reduce postprocedural myonecrosis after elective PCI in patients with stable angina.[19]

We found in the present study that triple-antiplatelet therapy plus bivalirudin strategy improved TMPG, was correlated with less MACE, and did not appear to raise the incidence of bleeding or thrombocytopenia in patients diagnosed with non-ST-segment elevation myocardial infarction who underwent PCI.

To our knowledge, this trial is the first research to show the effects of loading dose of cilostazol-based triple-antiplatelet therapy plus bivalirudin strategy in patients undergoing PCI. This investigation was designed to evaluate the clinical value of loading dose of cilostazol pretreatment prior to PCI. A recently published study showed that the loading dose of 200 mg cilostazol in addition to aspirin and clopidogrel improved platelet responsiveness to clopidogrel in the pre- and postprocedural phases and reduced the prevalence of high posttreatment platelet reactivity.[20] In the present study, loading dose of cilostazol-based triple-antiplatelet therapy plus bivalirudin strategy in patients undergoing PCI improved myocardial perfusion and prognosis.

Obviously, the present study had some limitations. Firstly, the duration of the study period was not long. Moreover, the changes in pharmacokinetic and pharmacodynamic profiles early after antiplatelet therapy probably have affected the outcomes. Secondly, the number of study subjects was too small to accurately evaluate the clinical efficacy and safety of the regimens. Thirdly, the study specifically focused on the patients who were diagnosed with non-ST-segment elevation myocardial infarction and who underwent PCI. A study concerning people with no cardiovascular risk factors and with cardiovascular risk factors should be done to further extend our results.

Considering that drugs currently approved to coat stents used in PCI do not discriminate between proliferating vascular smooth muscle cells (VSMCs) and endothelial cells (ECs), which delays reendothelialization and vascular healing, increasing the risk of late thrombosis following angioplasty, Santulli et al[21] developed a microRNA-based approach to inhibit proliferative VSMCs, thus preventing restenosis, while selectively promoting reendothelialization and preserving EC function. The results provide the basis for designing the next generation of selective therapy in PCI. The combination of a better stent platform and biodegradable polymer with this selective inhibition of VSMCs, without affecting ECs, has the potential to revolutionize the future of vascular interventional medicine.

Conclusion

Cilostazol-based triple-antiplatelet therapy improved TMPG and decreased MACE, and did not affect the incidence of bleeding or thrombocytopenia in non-ST-segment elevation myocardial infarction patients undergoing PCI.

Disclosure

The authors report no conflicts of interest in this work.

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