Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 47, No. 5, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.10.054

CLINICAL RESEARCH **Interventional Cardiology**

The Clinical Results of a Platelet Glycoprotein IIb/IIIa Receptor Blocker (Abciximab: ReoPro)-Coated Stent in Acute Myocardial Infarction

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OBJECTIVES This study is a prospective randomized trial investigating clinical outcomes of patients with acute myocardial infarction (AMI) treated with abciximab (ReoPro)-coated stents.

BACKGROUND Recently we have demonstrated that abciximab-coated stents have inhibitory effects in the prevention of coronary restenosis.

METHODS Ninety-six patients with AMI were randomly allocated into two groups; group I received abciximab-coated stents (n = 48, 57.1 ± 12.0 years), and group II received bare metal control stents (n = 48, 58.4 ± 11.6 years).

RESULTS At baseline, clinical characteristics, percent diameter stenosis, and minimal luminal diameter were no different between the two groups. One patient in group II had reinfarction and target lesion reintervention during hospital stay. Follow-up coronary angiography was obtained in 77.1% (37 of 48) in group I and 75.0% (36 of 48) in group II. Percent diameter stenosis and late loss were significantly lower in group I than group II (18.9 ± 5.54% vs. 37.9 ± 6.25%, p = 0.008; and 0.39 ± 0.29 mm vs. 0.88 ± 0.45 mm; p = 0.008, respectively). At follow-up intravascular ultrasound, intrastent lumen area and intrastent neointimal hyperplasia (NIH) area were 5.4 ± 1.8 mm^2 and 2.2 ± 1.5 mm^2, respectively, in group I and 4.3 ± 1.6 mm^2 and 3.4 ± 1.8 mm^2, respectively, in group II (p = 0.045). And, in-stent restenosis rate was lower in group I than group II (p = 0.011 and p = 0.008, respectively). During 1-year follow-up, two patients in group II (4.1%) had AMI, whereas no patient in group I suffered AMI. Target lesion revascularization and total major adverse cardiac events rates were relatively lower in group I compared with those in group II (10.4% [5 of 48] vs. 20.8% [10 of 48], p = 0.261, and 10.4% vs. 25.0%, p = 0.107, respectively).

CONCLUSIONS Abciximab-coated stent implantation was safe and effective without stent thrombosis in AMI patients. (J Am Coll Cardiol 2006;47:933–8) © 2006 by the American College of Cardiology Foundation

The development of coronary artery stenting reduces the incidence of acute coronary occlusion after percutaneous transluminal coronary angioplasty to <1% (1). In-stent restenosis caused by intimal hyperplasia, however, still occurs in as high as 10% of patients even after drug-eluting stent (DES) and thereby remains a significant clinical problem to be solved (2). It has been shown that stents coated with antiproliferative agents such as sirolimus and paclitaxel are associated with lower restenosis rates, after percutaneous coronary intervention (PCI), than conventional bare-metal stents. More recent reports have also shown the efficacy of these DES under more challenging conditions, such as small vessels, lesions of in-stent restenosis, diabetics, and long and complex lesions (3–7).

Abciximab, a potent antiplatelet agent that blocks the final pathways to platelet aggregation, improves outcomes of high-risk PCI and decreases the incidence of major adverse cardiac events (MACE) (8–11). Differently from other kinds of platelet glycoprotein IIb/IIIa receptor blockers, it also binds to Mac-1 (CD11b/18) on vascular endothelial cells and macrophages, thereby inhibiting inflammatory responses and smooth muscle cell proliferation after vascular injury (12–17). Recently, we demonstrated that abciximab-coated stents were safe and effective in the prevention of coronary restenosis in humans as well as in a porcine model (18,19).

The aim of the present study is to evaluate clinical and angiographic outcomes of abciximab-coated stent implantation in patients with acute myocardial infarction (AMI).

METHODS

Study group. Ninety-six patients with AMI who underwent PCI at Chonnam National University Hospital

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Manuscript received August 31, 2005; revised manuscript received October 10, 2005, accepted October 18, 2005.

JACC Vol. 47, No. 5, 2006
March 7, 2006:933–8

Abbreviations and Acronyms

AMI = acute myocardial infarction
DES = drug-eluting stent
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction

were recruited and then randomly divided into two groups: group I, which received abciximab-coated stents (n = 48), and group II, which received conventional bare-metal stents (n = 48). The inclusion criteria were AMI patients with age range from 18 to 80 years, target vessel diameter between 2.5 and 4.0 mm, lesion length <25 mm, and critical stenosis (>70%) on angiography. Patients with left main-stem stenosis, graft-vessel stenosis, cardiogenic shock, left ventricular ejection fraction <35%, or contraindications for antiplatelet agents were excluded from the study. The study protocol was reviewed and approved in sequence by the Korean Ministry of Health and Welfare and the Ethics Committee of Chonnam National University Hospital, and informed consent was obtained from all patients.

Manufacturing process of the abciximab-coated stent. Abciximab-coated stents were used according to the protocol previously described (18,19). Briefly, a plasma polymerization reaction was performed to attach amine radicals to the stent surface. For the attachment of amine radicals to the stent surface, diaminocyclohexane monomer was drifted to the tubular reactor in a constant dose, and plasma was generated with a radiofrequency power generator. The abciximab used was a human-murine chimeric antibody Fab fragment, ReoPro (Eli Lilly and Company, Indianapolis, Indiana). The carboxy radical of abciximab was introduced to the amine radicals attached to the stent to achieve covalent bonding and improved attachment power between the stent and abciximab. The abciximab coating on the surface of the stent was confirmed by scanning electron microscopy. For the release, kinetics of abciximab from the stent was done.

Study procedure, stent implantation, angiography, and IVUS. All other procedures were performed by standard techniques: randomly selected stents were deployed at 10 to 16 atmospheric pressure after predilation with a balloon catheter. In cases with residual stenosis, additional balloon dilatation was performed after stenting. None of the study patients received glycoprotein IIb/IIIa receptor blockers. All patients received aspirin (300 mg loading and 100 to 200 mg/day indefinitely) and clopidogrel (300 mg loading and 75 mg/day for 2 months). Heparin was administered as 5,000-U bolus, followed by 1,000 U/h and additional 5,000 U immediately before PCI to keep the activated clotting time (ACT) at 250 to 300 s. Successful PCI was defined as a patent vessel at the treatment site with anterograde Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 and angiographic residual stenosis <20% without occurrence of any cardiac events.

Acute myocardial infarction was defined as the presence of typical chest pain, ischemic change on the electrocardiogram in two or more contiguous leads, and peak elevation of plasma creatine kinase (CK) and CK-MB to at least twice normal. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion (TIMI flow grade 0 or 1) or thrombus within or adjacent to a previously successfully stented vessel (TIMI flow grade 1 or 2).

Bleeding events were classified as major, minor, or insignificant according to the criteria of the TIMI Study Group. Major bleeding events were defined as intracranial bleeding or a bleeding event that caused fall in hemoglobin of >4 g/dl or that required transfusion of >3 U of blood. Thrombocytopenia was defined as a platelet count $<100 \times 10^3/mm^3$.

Coronary angiography was performed at baseline, immediately after the procedure, and 6 months later. Quantitative diameter measurements of the coronary arteries were obtained by a blinded reviewer using a workstation with dedicated software (Philips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, the Netherlands) by a standard technique. In-stent restenosis was defined as an in-stent luminal diameter stenosis ≥40%. Late lumen loss was defined as the difference between the minimal luminal diameter immediately after stenting and the minimal luminal diameter at follow-up. The intravascular ultrasound (IVUS) imaging was performed in all patients before and after procedure and at follow-up. The IVUS images were acquired with motorized pullback at a constant speed of 1 mm/s (Galaxy, Boston Scientific, Natick, Massachusetts, or Endosonics, EndoSonics Corporation, Rancho Cordova, California).

Study end points. Clinical evaluation was done at 30 days, 6 months, and 1 year to assess patient symptom frequency and cardiac event rates. The primary end point was in-stent late lumen loss and the secondary end point was intrastent luminal volume by IVUS and composite of major cardiac events, including cardiac death, any myocardial infarction, and percutaneous or surgical revascularization of the target lesion 12 months after procedure.

Statistical analysis. We calculated that with a sample of 96 patients, the study would have 80% power to detect a difference in the mean late luminal loss of 0.30 mm between the two groups, assuming a standard deviation of 0.5 mm in each group, with the use of a two-group *t* test and a two-sided significance level of 0.5. All analyses were based on the intention-to-treat principle. For continuous variables, differences between the treatment groups were evaluated by analysis of *t* test. For categorical variables, differences were expressed as counts and percentages and were analyzed with the chi-square test. Statistical analysis was performed with the aid of commercially available software (SPSS Version 10.0, SPSS Inc., Chicago, Illinois).

Table 1. Baseline Clinical Characteristics

	Group I (n = 48) Abciximab-Coated Stent	Group II (n = 48) Control Stent	p
Age (yrs)	57.1 ± 12.0	58.4 ± 11.6	0.577
Men (%)	41 (85.4)	39 (81.3)	0.785
Risk factor (%)			
Current smoking	27 (56.3)	29 (60.4)	0.500
Hypertension	24 (50.0)	20 (41.7)	0.539
Hypercholesterolemia	10 (20.8)	12 (25.0)	0.809
Diabetes mellitus	9 (18.8)	10 (20.8)	1.00
Clinical diagnosis (%)			0.814
Non–ST-segment elevation MI	11 (22.9)	13 (27.1)	
ST-segment elevation MI	37 (77.1)	35 (72.9)	
Combined vascular disease (%)			
Peripheral	2 (4.2)	0 (0.0)	0.495
Non-hemorrhagic stroke	1 (2.1)	1 (2.1)	1.00
Hemorrhagic stroke	0 (0.0)	1 (2.1)	1.00
Family history	4 (8.3)	2 (4.2)	0.677
Previous coronary procedure (%)	1 (2.1)	1 (2.1)	1.00
Previous MI	1 (2.1)	0 (0.0)	1.00
Left ventricular function (%)			
Mean ejection fraction	58.8 ± 8.9	57.6 ± 11.1	0.654

MI = myocardial infarction.

RESULTS

Baseline clinical characteristics. Clinical characteristics for patients are shown in Table 1. No significant difference was observed in the clinical characteristics between the two groups. At presentation, ST-segment elevation myocardial infarction was diagnosed in 37 patients (77.1%) in group I and 35 (72.9%) in group II.

Procedural characteristics. Angiographic characteristics for patients are shown in Table 2. There were no differences between the two groups in the location of culprit vessels, lesion type, or number of diseased vessels. In all cases stent deployment was preceded by balloon predilation, and the diameter of used catheters was no different between the groups. Stent length was 18.0 ± 2.48 mm in group I and 18.2 ± 3.79 mm in group II. Stent diameter was 3.38 ± 0.37 mm in group I and 3.31 ± 0.36 mm in group II (Table 2). No significant bleeding or hemorrhagic events were observed in either group (Table 3).

Quantitative coronary angiography. Six-month angiographic follow-up was obtained in 37 patients (77.1%) in group I and in 36 (75.0%) in group II. In-stent restenosis was found in 5 patients (13.9%) in group I and 12 (34.3%) in group II (p = 0.045). Percentage of diameter stenosis was significantly lower in group I than group II (18.9 ± 5.54% vs. 37.9 ± 6.25%, p = 0.002). Late loss was also significantly lower in group I as compared with that in group II (0.39 ± 0.29 mm vs. 0.88 ± 0.45 mm, p = 0.008) (Table 4).

IVUS results. Serial IVUS measurements are shown in Table 5. Baseline stent and reference measurements were similar between the two groups. In the stented segment of the two groups from after-stent implantation to follow-up,

Table 2. Coronary Angiographic Characteristics

	Group I	Group II	p
Diseased vessels (%)			0.456
Right coronary artery	16 (33.3)	12 (25.0)	
Left anterior descending artery	26 (54.2)	26 (54.2)	
Left circumflex artery	6 (12.5)	10 (20.8)	
Diseased vessel number (%)			0.131
One-vessel	42 (87.5)	34 (70.8)	
Two-vessel	5 (10.4)	12 (25.0)	
Three-vessel	1 (2.1)	2 (4.2)	
ACC/AHA classification (%)			0.814
Type B1	37 (77.1)	35 (72.9)	
Type B2	11 (22.9)	13 (27.1)	
Pre-PCI TIMI flow (%)			0.223
TIMI flow grade 0	4 (8.3)	9 (18.8)	
TIMI flow grade 1	2 (4.2)	1 (2.1)	
TIMI flow grade 2	16 (33.3)	9 (18.8)	
TIMI flow grade 3	26 (54.2)	29 (60.4)	
Pre-dilation balloon (mm)			
Balloon length	20.0 ± 0.0	20.3 ± 1.7	0.314
Balloon size	3.34 ± 0.34	3.26 ± 0.36	0.137
Stent size (mm)	3.38 ± 0.37	3.31 ± 0.36	0.338
Stent length (mm)	18.0 ± 2.48	18.2 ± 3.79	0.282

ACC/AHA = American College of Cardiology/American Heart Association; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Table 3. Bleeding and Hematologic Complications After Stenting

	Group I	Group II	p
Major bleeding (%)	0	0	1.00
Intracranial hemorrhage (%)	0	0	1.00
Minor bleeding (%)			
Vascular access site (hematoma >5 cm)	0	0	1.00
Vascular access site (<5 cm)	1 (2.1)	1 (2.1)	0.131
Gingival bleeding	0	1 (2.1)	1.00
Gastrointestinal bleeding	0	0	1.00
Urinary tract bleeding	0	1 (2.1)	1.00
Any stroke (%)	0	0	1.00
Thrombocytopenia (<100,000 mm^3)	0	0	1.00

JACC Vol. 47, No. 5, 2006
March 7, 2006:933–8

Table 4. Quantitative Coronary Angiographic Results of Stented Segment

	Group I	Group II	p
Follow-up CAG number (%)	37 (77.1)	36 (75.0)	1.00
Restenosis rate (%)	5 (13.9)	12 (34.3)	0.045
Before stenting			
RD (mm)	2.95 ± 0.45	3.02 ± 0.51	0.751
MLD (mm)	0.91 ± 0.37	0.99 ± 0.41	0.418
DS (%)	70.7 ± 18.1	68.5 ± 15.1	0.214
Lesion length (mm)	10.7 ± 5.05	11.9 ± 4.89	0.745
Post-stenting			
RD (mm)	3.01 ± 0.41	2.99 ± 0.38	0.807
MLD (mm)	2.64 ± 0.51	2.62 ± 0.53	0.912
DS (%)	12.3 ± 7.40	14.1 ± 6.75	0.417
Follow-up			
MLD (mm)	2.23 ± 0.58	1.72 ± 0.59	0.008
DS (%)	18.9 ± 5.54	37.9 ± 6.25	0.002
Late loss (mm)	0.39 ± 0.29	0.88 ± 0.45	0.008

CAG = coronary angiogram; DS = diameter stenosis; MLD = minimal luminal diameter; RD = reference diameter.

there was a decrease in lumen cross-sectional area and an increase in neointimal hyperplasia area. A net decrease in lumen cross-sectional area was smaller in group I than in group II (2.2 ± 1.5 mm^2 vs. 3.4 ± 1.8 mm^2, p = 0.008), and a net increase in neointimal hyperplasia area was smaller in group I than in group II (2.2 ± 1.5 mm^2 vs. 3.4 ± 1.8 mm^2, p = 0.008).

In-hospital and follow-up results. During the hospital stay, one patient in group II had AMI as a result of acute thrombotic occlusion and underwent emergent revascularization. Complete clinical follow-up was available for 97.9% of the patients in both groups. One patient in group II had cardiac death. Two patients in group II (4.2%) had AMI, whereas no patient in group I suffered AMI. Target lesion revascularization was necessary in 5 patients (10.4%) in group I and 10 patients (20.8%) in group II; however, the incidence of overall MACE was relatively lower in group I than group II (n = 5 [10.4%] vs. n = 12 [25.0%]; p = 0.107) (Table 6).

DISCUSSION

The use of abciximab in patients with acute coronary syndrome was associated with reductions in the magnitude of rise in levels of circulating inflammatory markers after PCI. This anti-inflammatory effect of abciximab might be accounted for by the fact that it cross-reacts with Mac-1 (CD11b/18), a leukocyte integrin that mediates firm adhesion and transplatelet migration of leukocytes on vascular thrombus, thereby inhibiting inflammatory reactions occurring after vascular injury (15–17,20,21). Furthermore, except for other small molecular weight glycoprotein IIb/IIIa inhibitors, abciximab is known to bind to the vitronectin receptors found on platelets and vascular endothelial and smooth muscle cells and exert an inhibitory effect on migration and proliferation of smooth muscle cells after acute vessel injury (12–14). Coronary stenting in patients with AMI has problems to solve such as restenosis and reocclusion of infarct-related arteries.

This study is the first randomized, prospective clinical trial evaluating effects of abciximab-coated stents in patients with AMI. Patients who received abciximab-coated stents were free of procedure-related complications, and the incidence of in-hospital and 30-day MACE in this patient population was not significantly different when compared with patients who received uncoated control stents. Because all cases recruited for this study had not received PCI within 6 h, it is difficult to interpret our results in the same context as that of other primary PCI studies. In terms of restenosis

Table 5. Intravascular Ultrasound Results

	Group I	Group II	p
Preintervention			
Proximal reference EEM CSA (mm^2)	15.3 ± 3.1	15.2 ± 4.1	0.832
Lesion site EEM CSA (mm^2)	14.8 ± 3.7	14.3 ± 5.9	0.504
Lesion site lumen area (mm^2)	4.1 ± 0.9	3.7 ± 0.6	0.347
Lesion site plaque plus media CSA (mm^2)	10.7 ± 3.0	10.6 ± 5.6	0.880
Lesion site plaque burden (%)	72.3 ± 8.3	74.1 ± 10.3	0.619
Distal reference EEM CSA (mm^2)	13.7 ± 4.2	13.4 ± 3.8	0.604
Postintervention stent CSA (mm^2)	7.7 ± 2.4	7.8 ± 2.2	0.858
Follow-up			
Proximal reference EEM CSA (mm^2)	15.1 ± 3.5	15.0 ± 3.0	0.811
Lesion site EEM CSA (mm^2)	14.7 ± 3.8	14.3 ± 5.6	0.532
Stent CSA (mm^2)	7.6 ± 2.6	7.7 ± 2.4	0.878
Intrastent lumen area (mm^2)	5.4 ± 1.8	4.3 ± 1.6	0.011
Intrastent neointimal hyperplasia area (mm^2)	2.2 ± 1.5	3.4 ± 1.8	0.008
Distal reference EEM CSA (mm^2)	13.6 ± 4.8	13.5 ± 3.4	0.867
Serial (after intervention to follow-up) comparison			
Delta proximal reference EEM CSA (mm^2)	−0.2 ± 0.7	−0.2 ± 1.0	0.961
Delta stent cross-sectional area (mm^2)	−0.1 ± 1.3	−0.1 ± 1.1	0.968
Delta intrastent lumen area (mm^2)	−2.2 ± 1.5	−3.4 ± 1.8	0.008
Delta intrastent neointimal hyperplasia area (mm^2)	2.2 ± 1.5	3.4 ± 1.8	0.008
Delta distal reference EEM CSA (mm^2)	−0.1 ± 1.2	0.1 ± 1.4	0.967

CSA = cross-sectional area; EEM = external elastic membrane.

Table 6. In-Hospital Primary Outcomes After Stenting

	Group I (n = 48)	Group II (n = 48)	p
Success rate (%)	48 (100)	48 (100)	1.00
Primary end points (%)			
Cardiac death	0 (0.0)	0 (0.0)	1.00
Acute myocardial infarction	0 (0.0)	1 (2.1)	1.00
Emergent revascularization	0 (0.0)	1 (2.1)	1.00
Emergent bypass surgery	0 (0.0)	0 (0.0)	1.00
Clinical follow-up number	47 (97.9)	47 (97.9)	
Total follow-up MACE	5 (10.4)	12 (25.0)	0.107
Cardiac death	0 (0.0)	1 (2.1)	1.00
Acute myocardial infarction	0 (0.0)	2 (4.2)	0.495
TLR	5 (10.4)	10 (20.8)	0.261
Symptomatic angina	1 (2.1)	5 (10.4)	0.204
CABG	0 (0.0)	0 (0.0)	1.00

CABG = coronary artery bypass graft; MACE = major adverse cardiac events; TLR = target lesion revascularization.

and target lesion revascularization rates, however, our results (13.9% and 10.4%, respectively) were superior to those of the Stent PAMI (22) trial (20.3% and 7.7%) or the CADILLAC (23) study (22.2% and 8.9%), which compared outcomes of stenting in AMI patients. Moreover, these results are less favorable compared with those of sirolimus-eluting stent implantation by Saia et al. (24) (late loss: -0.04 ± 0.25 mm) and Lemos et al. (25) (target lesion revascularization rate: 1.1%; MACE rate: 9.4%). The incidence of overall MACE was lower in the abciximab-coated stent group, which was primarily attributed to a decrease in the incidence of AMI. In fact, as was suggested by Jeremia et al. (26), who reported that the incidence of stent thrombosis after sirolimus-eluting stent implantation was only 1.1%, which is similar to that after conventional stenting, acute or subacute stent thrombosis associated with drug-eluting stent implantation is not thought to be clinically significant.

Although the patient number was relatively small, the absence of episodes of AMI by acute or subacute thrombotic occlusion during one-year clinical follow-up in the patients who received abciximab-coated stents suggests that platelet aggregation was effectively inhibited with use of abciximab, and this effect could be maintained for a long-term period. Postprocedural clopidogrel was given for two months according to the same protocol for conventional stenting, whereas it was prescribed for a more prolonged period of time in the trials using DES. Abciximab-coated stent implantation was not associated with significant bleeding complications. No patient in either group received platelet glycoprotein IIb/IIIa blockers during PCI, and there was no difference in the postprocedural antiplatelet regimen between the two groups.

One of the main limitations of this study is that PCI was not performed at least within 6 h of onset of chest pain in all cases, whereby the true effects of abciximab-coated stents in AMI might have been rendered less pronounced. And then, this clinical study included only 98 patients with de novo, single vessel stenting, and follow-up coronary angiogram was performed in only 75% to 77% patients. Furthermore, it is only a single center study.

In conclusion, abciximab-coated stents in AMI patients were feasible and safe. Low rates of restenosis and revascularization were observed. At one-year clinical follow-up, these results appear to be sustained. These observations warrant further investigation with a large, randomized multicenter study.

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