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Effect of Cilostazol on In-Stent Neointimal Hyperplasia After Coronary Artery Stenting

— A Quantitative Coronary Angiography and Volumetric Intravascular Ultrasound Study —

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Background This study was designed to investigate the efficacy of cilostazol on the prevention of in-stent neointimal hyperplasia as measured by both quantitative coronary angiography (CAG) and volumetric intravascular ultrasound (IVUS).

Methods and Results Fifty-nine patients (39 men, age 62 years) undergoing elective coronary stenting were randomly assigned to receive aspirin plus clopidogrel or ticlopidine (Group I, n=28, 30 lesions) or aspirin plus clopidogrel or ticlopidine plus cilostazol (Group II, n=31, 35 lesions). CAG and IVUS were performed and repeated at 6 months to assess the primary endpoints of minimal luminal diameter (MLD) and in-stent neointimal hyperplasia volume. Follow-up CAG was performed on all patients and follow-up IVUS study was available for 50 lesions in 48 patients (24 lesions in Group I, 26 in Group II). There were no significant differences in the baseline angiographic data between the 2 groups. At 6 months follow-up, in-stent MLD was 1.90±0.76 mm in Group I and 2.41±0.85 mm in Group II (p=0.006). Volumetric IVUS at 6 months demonstrated that in-stent intimal hyperplasia volume per stent length was 2.2±1.4 mm^3/mm in Group I and 1.0±0.5 mm^3/mm in Group II (p=0.001).

Conclusions Triple antiplatelet therapy including cilostazol seems to be more effective at preventing in-stent neointimal hyperplasia than a dual antiplatelet regimen. (*Circ J* 2007; **71:** 1685 – 1690)

Key Words: Cilostazol; Coronary stents; Interventional therapy; Restenosis; Ultrasonography

In-stent restenosis, mainly attributable to neointimal hyperplasia, remains a major limitation of coronary stenting.[1–4] Various pharmacological therapies, designed to inhibit coronary stent restenosis, have been tried, but most have failed to demonstrate a clinically significant impact.[5–8]

Cilostazol, a potent antiplatelet agent that selectively inhibits phosphodiesterase type III, has a broad range of pharmacological effects in addition to inhibiting platelet aggregation.[9] Animal studies have suggested that cilostazol reduces smooth muscle proliferation[10] and intimal hyperplasia following endothelial injury.[11] Several clinical trials have demonstrated that cilostazol has a comparable or better ability to prevent restenosis after balloon angioplasty[12] or stent implantation when compared with aspirin or ticlopidine.[13–17] Recently, the addition of cilostazol to a conventional antiplatelet regimen was shown to result in a significantly larger minimal luminal diameter (MLD) and a significantly lower binary restenosis rate at 6 months after coronary stenting.[18] However, in that study, the reduction in angiographically determined late loss was not confirmed by intravascular ultrasound (IVUS).

Consequently, we performed a prospective, randomized trial in patients undergoing elective coronary artery stenting to determine the efficacy of triple antiplatelet therapy including cilostazol, as compared with dual antiplatelet therapy, for the prevention of in-stent neointimal hyperplasia as measured by quantitative coronary angiography (QCA) and IVUS.

Methods

Study Design and Patient Selection

Fifty-nine patients with significant stenosis in a native coronary artery who were undergoing elective coronary stent implantation were included in this prospective, randomized study. All patients were recruited at the Yonsei Cardiovascular Center, Yonsei University College of Medicine, Seoul, Korea. Exclusions to this study were as follows: patients who underwent primary angioplasty for acute ST-elevation myocardial infarction (MI); long lesion that could not be completely covered by a single stent; chronic total occlusion; lesions with moderate to severe calcification; contraindications to treatment with antiplatelet agents; impaired liver function (aspartate aminotransferase or alanine aminotransferase 2.5-fold above upper normal limits); renal insufficiency with a serum creatinine value >2.5 mg/dl;

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Table 1 Baseline Characteristics of the Study Population

	Dual antiplatelet therapy group (n=28)	*Triple antiplatelet therapy group (n=31)*	*p value*
Age, years	*61±9*	*63±10*	*0.382*
Male	*17 (61%)*	*22 (71%)*	*0.425*
Diabetes	*8 (29%)*	*7 (23%)*	*0.766*
Hypertension	*17 (61%)*	*20 (65%)*	*0.793*
Current smoker	*12 (43%)*	*19 (61%)*	*0.196*
Hypercholesterolemia (total cholesterol >200 mg/dl)	*4 (14%)*	*8 (26%)*	*0.342*
Medication			
Ticlopidine	*15 (54%)*	*17 (55%)*	*0.922*
Clopidogrel	*13 (46%)*	*14 (45%)*	*0.922*
Statin	*16 (57%)*	*19 (61%)*	*0.746*
Clinical diagnosis			*0.734*
Stable angina	*13 (46%)*	*14 (45%)*	
Unstable angina	*9 (32%)*	*8 (26%)*	
Non ST-elevation MI	*6 (21%)*	*9 (29%)*	

MI, myocardial infarction.

congestive heart failure or severe left ventricular dysfunction (ejection fraction <30%).

Patients scheduled for angioplasty were randomly selected for either the dual antiplatelet therapy group (aspirin plus clopidogrel or ticlopidine) or the triple therapy group (aspirin plus clopidogrel or ticlopidine plus cilostazol) before stent implantation was attempted. Patient randomization was performed by the study coordinator, based on a blocked design randomization scheme. Aspirin and clopidogrel (or ticlopidine) therapy was started at least 2 days prior to stenting in all patients. Maintenance dosing for each antiplatelet agent was 100 mg daily for aspirin, 75 mg daily for clopidogrel, and 250 mg twice daily for ticlopidine. Either clopidogrel or ticlopidine was administered for 1 month after stenting, whereas aspirin was continued indefinitely after the procedure. In the triple therapy group, cilostazol (100 mg twice daily) treatment was initiated within 6 h of stent implantation and continued until the 6 months follow-up angiography.

Following primary intervention, patients were contacted at 1 month, returned for a clinic visit at 3 months, and were scheduled for repeat angiography, including IVUS, at 6 months. Patients were monitored at these times for the occurrence of adverse cardiac events, bleeding complications, and drug side-effects.

The study was conducted according to the principles of the Declaration of Helsinki and all patients gave written, informed consent prior to randomization.

Angioplasty Procedure

Before the procedure all patients received a bolus of 10,000 U of heparin. If necessary, a repeat bolus of heparin (5,000 U) was given to maintain an activated clotting time of >300 s. Balloon angioplasty and stent implantation were performed according to standard techniques via a femoral approach. According to the study protocol, patients received only Express Stents (Boston Scientific Corp, Natick, MA, USA).

IVUS Imaging Protocol

IVUS was performed post-intervention to ensure complete strut apposition and at 6 months afterwards, during the follow-up angiography, for quantitative analysis. After intracoronary administration of 0.2 mg nitroglycerin, IVUS imaging was performed using a motorized transducer pullback system at 0.5 mm/s and a commercial scanner (Boston Scientific Scimed) consisting of a 30-MHz transducer within a 3.2Fr imaging sheath.

IVUS Analysis

Quantitative volumetric IVUS analysis was performed off-line with a computer-based analysis system (Echoplaque 2; INDEC Systems Inc, Mountain View, CA, USA) by an individual who was unaware of the patients' treatment assignments. Total plaque volume, plaque volume behind the stent, and neointimal formation were calculated as total vessel volume minus lumen volume, total vessel volume minus stent volume, and stent volume minus lumen volume, respectively. To account for differences in stent length, all IVUS parameters were calculated per millimeter of stent length for the stented segment.

QCA

Angiographic measurements were done with an offline QCA system (ANCOR 2.3; Siemens, Munich, Germany) by an individual who was unaware of the patients' treatment assignments. A contrast-filled nontapered catheter tip was used for calibration. QCA before and after stent implantation, as well as at follow-up, was performed in the same projections of the treated lesion after administration of intracoronary nitroglycerin. MLD, reference diameter, percent diameter stenosis, and lesion length were measured. To assess MLD, the most severe stenosis in 2 orthogonal views was measured. Acute gain was defined as the difference in MLD before and immediately after intervention. Late loss was calculated as the difference in MLD immediately after intervention and at follow-up. Loss index was defined as the ratio of late loss to acute gain.

Endpoints of the Study and Definitions

The primary endpoints were MLD as assessed by QCA, and the extent of neointimal volume as assessed by IVUS, at 6 months follow-up. Events monitored during clinical follow-up included stent thrombosis, bleeding complications, death, MI, and target vessel revascularization (TVR). Subacute stent thrombosis was defined as angiographically confirmed thrombotic occlusion of the stented segment within 30 days after the index hospitalization. Late stent thrombosis was defined as any stent thrombosis event during the period of 30 days to 1 year after stent implantation. Major bleeding was defined as the need for transfusion or surgery. MI was diagnosed when creatine kinase-MB was

Table 2 Baseline Angiographic and Procedural Data

	Dual antiplatelet therapy group (n=30 lesions)	Triple antiplatelet therapy group (n=35 lesions)	p value
Targeted coronary artery			0.536
Left anterior descending	19 (63%)	18 (51%)	
Left circumflex	4 (13%)	6 (17%)	
Right coronary	7 (23%)	11 (31%)	
AHA/ACC lesion type			0.326
A	0	2 (6%)	
B1	9 (30%)	11 (31%)	
B2	17 (57%)	14 (40%)	
C	4 (13%)	8 (23%)	
Small vessel (<3.0 mm)	13 (43%)	13 (37%)	0.623
Maximal inflation pressure (atmospheres)	14.94±3.24	14.30±2.36	0.485

AHA, American Heart Association; ACC, American College of Cardiology.

Table 3 Angiographic QCA Data

	Dual antiplatelet therapy group (n=30 lesions)	Triple antiplatelet therapy group (n=35 lesions)	p value
Baseline			
Lesion length (mm)	17.53±5.52	15.32±5.69	0.113
Reference diameter (mm)	3.09±0.50	3.16±0.48	0.727
Minimal luminal diameter (mm)	0.85±0.47	0.74±0.43	0.304
%diameter stenosis	73.47±13.59	76.30±13.80	0.324
After Intervention			
Balloon-to-artery ratio	1.10±0.13	1.11±0.12	0.891
Stent diameter (mm)	3.37±0.39	3.46±0.45	0.354
Stent length (mm)	18.80±4.35	18.14±4.78	0.567
MLD (mm)	2.98±0.47	3.10±0.50	0.425
%diameter stenosis	4.01±5.07	2.24±4.52	0.069
Follow-up			
Follow-up interval (months)	6.1±0.6	6.1±0.6	0.980
Reference diameter (mm)	2.96±0.44	3.04±0.47	0.493
MLD (mm)	1.90±0.76	2.41±0.85	0.006
%diameter stenosis	35.19±25.52	21.57±23.83	0.008
Late loss (mm)	1.08±0.80	0.69±0.69	0.031
Loss index	0.52±0.37	0.30±0.33	0.005
Binary restenosis	8 (27%)	4 (11%)	0.197

QCA, quantitative coronary angiography; MLD, minimal luminal diameter.

elevated by more than 3-fold.

Statistical Analysis

For continuous variables, results are presented as the mean±SD. Differences in categorical variables were analyzed by the Fisher exact probability test, and differences in continuous variables were evaluated by comparison between 2 groups, using the Mann-Whitney U-test. Because the sample size was small and parameters are not distributed normally, nonparametric tests were chosen. Angiographic and procedural characteristics, as well as IVUS measurements, were determined using lesion-based assessment. A 2-sided value of $p<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 11.0 (SPSS Inc, Chicago, IL, USA).

Results

Baseline Clinical Characteristics

The 59 patients (age 62±9 years, range 36–82) were randomized to receive either dual antiplatelet therapy (30 lesions in 28 patients) or triple antiplatelet therapy (35 lesions in 31 patients). Both groups did not significantly differ with respect to baseline characteristics (Table 1).

Angiographic and Procedural Results

There were no significant differences in the target vessels or lesion characteristics between the 2 groups (Table 2). All patients received unfractionated heparin. Both groups were treated uniformly with regard to stenting. In all lesions, a single Express stent (Boston Scientific Corp) was used. Deployment pressures, final percent stenosis, and final MLD were similar (Table 3). IVUS after the intervention revealed complete stent apposition to the vessel wall in all lesions.

Clinical Follow-up

Six-month clinical follow-up (6.1±0.6 months) was conducted for all patients in both groups. There were 8 cases of TVR during the 6 months follow-up, 4 in each group ($p=0.816$). Of the 8 patients with angiographic restenosis in the dual antiplatelet therapy group, TVR was performed in 4 clinically indicated cases. No cases of death, MI, or subacute stent thrombosis were recorded during the study. Late stent thrombosis was not observed during the follow-up period. Neither major bleeding nor drug side-effects such as neutropenia or thrombocytopenia were found in either group. Every patient in the triple antiplatelet therapy group continued taking cilostazol until 6 months follow-up, all without the occurrence of side-effects such as headache or palpitation.

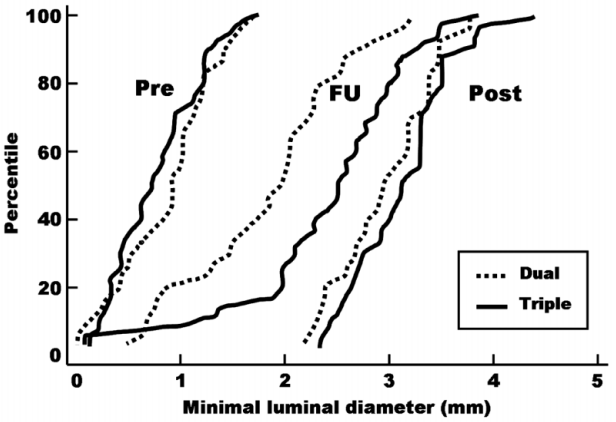

Fig 1. Cumulative distribution curves for minimal luminal diameter in both groups before intervention (Pre), immediately after stent implantation (Post), and at 6 months follow-up (FU). At 6 months, the mean degree of minimal luminal diameter in the group that received triple antiplatelet therapy, which included cilostazol, was significantly greater than in the dual antiplatelet group (2.41±0.85 mm vs 1.90±0.76 mm, p=0.006).

Angiographic and IVUS Data at 6-Month Follow-up

Follow-up angiography at 6 months was completed in all patients. Results of QCA at 6 months are detailed in Table 3. The MLD of the stented segments was significantly larger in the triple antiplatelet therapy group compared with the dual therapy group (2.41±0.85 mm vs 1.90±0.76 mm, p=0.006) because of significantly less late loss in the former group (Fig 1). However, there was no significant difference in the binary restenosis rate (≥50% luminal narrowing) between the 2 groups.

Follow-up IVUS studies were performed on 50 lesions in 48 patients (24 lesions in the dual group, 26 in the triple group). There were no significant differences with respect to baseline characteristics and procedural data between those with and without IVUS follow-up. As shown in Table 4, compared with the dual therapy group triple antiplatelet therapy significantly reduced neointimal volume within the stented segment (1.0±0.5 mm^3/mm vs 2.2±1.4 mm^3/mm; p=0.001), leading to a significantly larger luminal volume.

Discussion

This prospective, randomized study demonstrated that including cilostazol in triple antiplatelet therapy lead to a reduction in neointimal hyperplasia after coronary bare metal stent implantation in patients with native coronary artery disease.

The anti-restenotic effect of cilostazol has been reported in several clinical trials[13–18] all of which report comparable or superior ability of cilostazol in preventing restenosis when compared with ticlopidine. Recently, the Cilostazol for Restenosis Trial, a large-scale, randomized, double-blinded study, demonstrated that adding cilostazol to a conventional antiplatelet regimen reduces the risk of restenosis after coronary stent implantation as evaluated by QCA. Moreover, this outcome was accomplished without an increase in adverse effects![18]

Our QCA data also showed a significantly larger MLD at the 6 months follow-up in the triple antiplatelet therapy group as compared with the dual therapy group, because of significantly less late loss in the former group. Owing to the small sample size, the binary restenosis rate was not significantly different between the 2 groups. Volumetric IVUS confirmed that the addition of cilostazol significantly reduced in-stent neointimal tissue proliferation when compared with conventional antiplatelet therapy. It has been reported that in-stent restenosis is influenced by various factors related to the lesion and the procedure![19–23] In this study, angiographic characteristics such as target vessel, lesion length, vessel diameter, and post procedural MLD were not significantly different between the groups. Maximal inflation pressure and the balloon-to-artery ratio, considered to be an index of coronary injury, were also similar in both groups. Furthermore, all patients received the same type of stent (Express; Boston Scientific Corp) and those with overlapping stents were excluded from this study. Therefore, it is unlikely that the differences in either the lesional or procedural characteristics accounted for the effect on neointimal proliferation.

Regarding the safety of the triple antiplatelet regimen, major bleeding or drug side-effects were not observed in this study. Although it is likely this result is related to our small sample size, recent studies have shown that adding cilostazol to aspirin and ticlopidine or clopidogrel does not increase major bleeding or the incidence of adverse drug

Table 4 Volumetric IVUS Data

	Dual antiplatelet therapy group (n=24 lesions)	*Triple antiplatelet therapy group (n=26 lesions)*	*p value*
After intervention			
Total vessel volume	*13.2±3.6*	*14.5±4.4*	*0.298*
Stent volume	*6.7±2.0*	*7.0±2.3*	*0.716*
Lumen volume	*6.7±2.0*	*7.0±2.3*	*0.716*
Follow-up			
Follow-up interval (months)	*6.1±0.5*	*6.2±0.6*	*0.490*
Total vessel volume	*12.9±3.5*	*14.3±4.5*	*0.368*
Stent volume	*6.5±2.0*	*6.8±2.3*	*0.691*
Lumen volume	*4.3±1.6*	*5.8±2.2*	*0.028*
Neointimal volume	*2.2±1.4*	*1.0±0.5*	*0.001*
Serial (after intervention to follow-up) comparison			
ΔTotal vessel volume	*–0.3±0.5*	*–0.3±0.4*	*0.998*
ΔStent volume	*–0.2±0.2*	*–0.1±0.2*	*0.347*
ΔLumen volume	*–2.4±1.4*	*–1.2±0.4*	*<0.001*

IVUS, intrarvascular ultrasound.
IVUS parameters are given in mm^3 per 1-mm stented segment.

reactions![18,24,25]

The exact mechanism by which triple antiplatelet therapy results in reduced neointimal tissue proliferation remains unclear. Cilostazol decreases the activity of phosphodiesterase type III, leading to the accumulation of cyclic adenosine monophosphate. The inhibitory action of cilostazol on neointimal formation and restenosis seems to be the result of its ability to block vascular smooth muscle cell growth and stimulate hepatocyte growth factor production, which, in turn, accelerates regeneration of endothelial cells![26]

Study Limitations

The major limitation is the small sample size. Therefore, future studies with a larger sample are needed to elucidate the effects of cilostazol in various subgroups and to determine whether the anti-restenotic effects of cilostazol translate into clinical benefits, such as the reduction of TVR. In addition, the randomization in this study was not blinded, but all endpoints were adjudicated by physicians who were unaware of the patients' treatment assignments.

The recent introduction of drug-eluting stents has been shown to significantly reduce restenosis but not eliminate it![27–29] Therefore, complementary anti-restenotic therapies maintain an important role. In addition to cilostazol, some encouraging results have been found with oral drugs such as thiazolidinediones or oral rapamycin, illuminating the value of this approach to reduce restenosis![18,30–32] Until now, however, no data have been available regarding the antiproliferative effect of cilostazol in patients receiving drug-eluting stents. The role of effective adjunctive pharmacologic therapy to prevent in-stent restenosis in the drug-eluting stent era may deserve further evaluation in future trials.

Conclusions

Compared with a dual antiplatelet regimen, including cilostazol in triple antiplatelet therapy seems to more effectively prevent in-stent neointimal hyperplasia after coronary bare metal stent implantation in patients with native coronary artery disease.

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