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Effects of Cilostazol on Late Lumen Loss After Palmaz-Schatz Stent Implantation

Masao Yamasaki, MD, Kazuhiro Hara,* MD, Yuji Ikari, MD, Nobuyuki Kobayashi, MD, Ken Kozuma, MD, Yuki Ohmoto, MD, Yoshio Oh-Hashi, MD, Junya Ako, MD, Hiroyoshi Nakajima, MD, Noriyasu Chiku, MD, Fumihiko Saeki, MD, and Tsutomu Tamura, MD

Cilostazol inhibits intimal hyperplasia after stent implantation into canine iliac arteries. To determine the antiproliferative effect of this agent, cilostazol or aspirin was randomly given for 6 mo to 36 patients treated with Palmaz-Schatz stent implantation. Initial success was obtained in 34 patients. Repeat angiography was performed in 33 patients, and the complete angiographic data were obtained in 22 lesions of the cilostazol group and in 21 lesions of the aspirin group. The reference diameter and minimal luminal diameter were similar in both groups before and immediately after stent implantation. At follow-up, minimal luminal diameters were significantly greater in the cilostazol group than in the aspirin group ($P < 0.001$). Late loss and loss index were significantly smaller in the cilostazol group than in the aspirin group ($P < 0.001$). These results suggest that cilostazol reduces angiographic late lumen loss and thereby may reduce the incidence of restenosis after Palmaz-Schatz stent implantation. *Cathet. Cardiovasc. Diagn. 44:387–391, 1998.*

Key words: quantitative coronary angiography; restenosis; antiplatelet agent

INTRODUCTION

The restenosis rate after coronary intervention has been reduced by Palmaz-Schatz stent implantation in patients with de novo lesions in the native coronary artery or in patients with saphenous vein graft disease [1–3]. However, restenosis still occurs in 15–40% of patients, and therefore, restenosis remains a major limitation of coronary stenting [4,5].

Cilostazol (Ohtsuka Pharmaceutical Company, Tokushima, Japan) has been developed in Japan as an antiplatelet agent [6]. Its antiplatelet and vasodilating actions have been attributed to an increase in the intracellular concentration of cAMP [7]. Recently, Takahashi et al. [8] reported that micromolar concentrations of cilostazol inhibit the incorporation of [^{3}H] thymidine into DNA and also inhibit cell growth in cultures of rat aortic arterial smooth muscle cells stimulated with platelet-derived growth factor, insulin, and insulin-like growth factor. Subsequently, Kubota et al. [9] found an inhibitory effect of cilostazol on intimal hyperplasia following the implantation of a Gianturco stent into the canine iliac artery. The present study was undertaken to determine whether these antiplatelet and antiproliferative effects of cilostazol altered the process of luminal renarrowing in patients treated with Palmaz-Schatz stent implantation.

METHODS

Patients

From October 1994 to March 1995, 100 patients were treated with 150 coronary stents at our hospital. Thirty-six patients receiving elective stent implantation were enrolled into a prospective randomized open-label study. All patients gave written informed consent as approved by our hospital committee. Both patients with native coronary artery and patients with saphenous vein graft lesions were included in this study. Patients with acute coronary syndrome were excluded unless their conditions were stabilized. Eighteen patients were allocated to each of the cilostazol and aspirin groups. One patient in the aspirin group was withdrawn because he was found to have left main disease at time of intervention. He underwent bypass surgery without any complications. Thirty were men (86%). Their mean age was 61 years (SD, 8.8). Twenty (57%) of the 35 patients had prior coronary revascularization.

Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan

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*Correspondence to: Dr. Kazuhiro Hara, Division of Cardiology, Mitsui Memorial Hospital, 1 Kanda Izumicho, Chiyoda-ku, Tokyo 101, Japan. E-mail: khara@ff.iij4u.or.jp

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Palmaz-Schatz Stent Implantation

The Palmaz-Schatz (PS) stent (Johnson & Johnson Interventional Systems, Warren, NJ), 15 mm in length and with 1 mm of articulation, was used in this study. Our protocol of PS stent implantation has been described previously [10]. The size of the stent was determined by measuring the reference diameter of the lesion using the online quantitative coronary angiography (QCA) system (Cathex Coronary Image Processor-310, Cathex, Inc., Tokyo, Japan) [10]. The stent was placed either by the stent delivery system (Johnson & Johnson Interventional Systems) or was mounted on the balloon used for predilatation. After successful delivery, balloon dilatation at high pressure ($\geq$14 atmospheres) was added in order to achieve our goal of a residual stenosis of $<$10%.

Study Protocol

All 35 patients were taking aspirin, 182–330 mg PO daily, before the intervention. Heparin (100 units per kg weight) was administered intravenously before the intervention, followed by drip infusion to maintain an activated clotting time of $>$200 sec, until prothrombin time reached at least 16 sec. Warfarin was started the next day and was continued for 1 month. Eighteen patients received cilostazol 200 mg PO daily, beginning on the day of stenting. Aspirin was discontinued in these patients. The other 17 patients were maintained on aspirin (243 mg per day). If patients had a headache or other side effects possibly due to cilostazol, cilostazol was replaced with aspirin. Follow-up was obtained at clinic visits. The occurrence of side effects, including headache, flushing, hypotension, and changes in liver function, were monitored for 6 mo. Follow-up coronary angiograms were obtained at a mean of 6 mo after the intervention. Coronary angiograms were taken before and after intervention as well as at 6-mo follow-up after oral or intracoronary administration of nitroglycerin. This study was approved by our Institutional Review Board, and informed consent was provided by all patients.

Angiographic Analysis

Coronary angiograms were analyzed in the unblinded fashion using a offline QCA system (Cathex Coronary Image Processor-310, Cathex, Inc.). The frames were projected onto a cine 35-mm viewer optically coupled to a video camera. The video signal was digitized onto a computer. The pixel matrix was 640 $\times$ 512 in a frame memory. The density level was 8 bits. With this system, the region of interest, which included a segment of angiographically normal vessel proximal and distal to the stenosis, was defined. After identification of the beginning and end of the segment to be analyzed, the center line was determined automatically. The segment contour was computed with the weighted sum of the first and second derivative functions. By using the guide catheter as a scaling device, absolute measurements in millimeters were determined. The same orthogonal views were selected to measure the minimal luminal diameter (MLD). MLDs were compared in the same view, before and immediately after stenting, and again at the 6-mo follow-up. In repeated analysis of a random sample of 20 angiograms on patients undergoing angioplasty, the intraobserver variation for measurements of MLD was 0.01 mm in accuracy and 0.06 mm in precision, and the interobserver variation was 0.01 mm in accuracy and 0.14 mm in precision.

The acute gain, late loss, net gain, and loss index were calculated, and mean values were compared between the two groups [11]. Acute gain was calculated as the difference between the pre- and post-MLDs, late loss as the difference between the post-MLD and the follow-up MLD, and net gain as the difference between the pre-MLD and the follow-up MLD. The loss index was the ratio of late loss to acute gain.

TABLE I. Patient Characteristics*

Characteristics	Cilostazol	Aspirin	Total
N	18	17	35
Age (yr)	62 $\pm$ 9	61 $\pm$ 9	61 $\pm$ 9
M/F	17/1	13/4	30/5
Prior MI	9	10	19 (54%)
Prior CABG/BA	9	11	20 (57%)
Unstable angina	2	2	4 (11%)
Multivessel disease	6	7	13 (37%)
Hypertension	8	6	14 (42%)
Diabetes mellitus	2	4	6 (17%)
High cholesterol	6	5	11 (31%)

*MI, myocardial infarction; CABG, coronary artery bypass surgery; BA, balloon angioplasty.

Statistical Analysis

Data are reported as means $\pm$ SD. Student's t-test was used for group comparisons. A level of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Demographics and clinical characteristics did not differ between the two groups (Table I). Characteristics of the lesions are shown in Table II. There were no differences between groups in location of the lesion, lesion morphology, number of restenotic lesions, or mean reference diameter.

Initial and Follow-Up Results

Initial success was obtained in 34 (97%) of 35 patients. One patient in the aspirin group was withdrawn because

TABLE II. Lesion Characteristics*

Characteristics	Cilostazol	Aspirin	Total
N	22	23	45
Location			
LAD	8	9	17 (38%)
LCX	4	2	6 (13%)
RCA	9	9	18 (40%)
SVG	1	3	4 (9%)
Morphology			
AHA (A/B/C)	4/16/2	1/19/3	
Long (>20 mm)	5	8	13 (29%)
Eccentric	21	21	42 (93%)
Calcification	2	6	8 (18%)
No. of restenotic lesions	5	5	10 (22%)
Reference diameter (mm)	3.09 ± 0.38	3.10 ± 0.33	

*LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SVG, saphenous vein graft; AHA, AHA classification of morphology.

of guide wire failure. All patients were discharged uneventfully. All 18 patients in the cilostazol group could continue to take medications without any side effects. There were no subacute occlusions or other complications in the cilostazol group. One patient in the aspirin group had a totally occluded saphenous vein graft at 6-mo follow-up. Two lesions in this vein graft were withdrawn from this angiographic analysis. One patient in the cilostazol group was withdrawn because progressive renal failure precluded a second angiogram. Therefore, 2 of 35 patients did not undergo follow-up angiography, but they were free of angina during the follow-up period. Complete clinical and angiographic data were obtained in 33 patients (43 lesions). Three patients in the aspirin group but none in the cilostazol group had recurrent symptom or myocardial ischemia during follow-up.

Angiographic Analysis

Figure 1 shows changes in MLDs in both groups. There were no differences in MLDs after intervention between the groups. MLDs at 6-mo follow-up were significantly greater in the cilostazol group than in the aspirin group. Mean diameter stenoses after intervention were similar in both groups (8 ± 10% in the cilostazol group and 6 ± 10% in the aspirin group).

The acute gain, late loss, and net gain for each group are listed in Table III. The acute gain in both groups was similar, but a significantly lower late loss and a greater net gain were observed in the cilostazol group as compared to the aspirin group ($P < 0.001$). The mean loss index was 0.23 in this study. This loss index was significantly lower in the cilostazol group than in the aspirin group ($P < 0.001$) (Fig. 2).

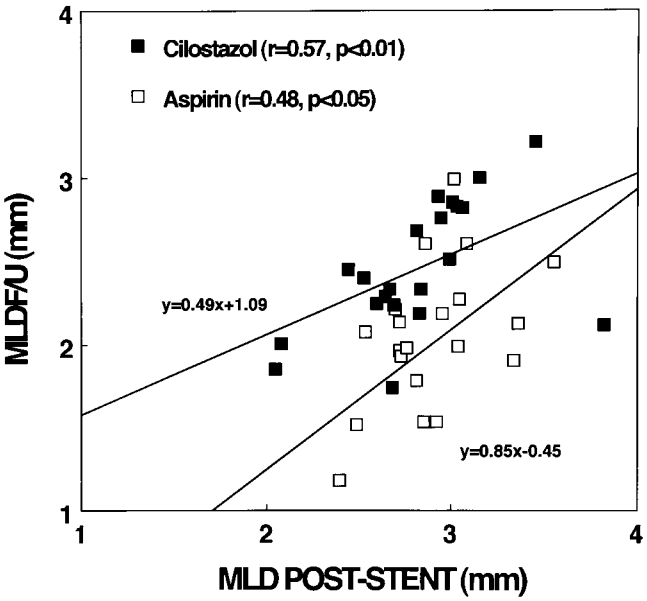

Fig. 1. Changes of minimal luminal diameter between just after the procedure and at follow-up. ■, Cilostazol group, n = 22; □, aspirin group, n = 21.

TABLE III. Effect of Cilostazol on Changes in Minimal Luminal Diameter*

	Cilostazol	Aspirin	*P*
N	22	21	
Pre-MLD	1.16 ± 0.51	1.46 ± 0.38	n.s.
Post-MLD	2.87 ± 0.47	2.88 ± 0.29	n.s.
F/u MLD	2.49 ± 0.40	1.99 ± 0.51	<0.05
Acute gain (mm)	1.72 ± 0.65	1.42 ± 0.41	n.s.
Late loss (mm)	0.39 ± 0.40	0.90 ± 0.45	<0.001
Net gain (mm)	1.33 ± 0.61	0.53 ± 0.67	<0.001

*MLD, minimal luminal diameter; F/u, at 6-mo follow-up.

DISCUSSION

Results of this study showed that the loss index was significantly smaller in patients treated with cilostazol as compared to those treated with aspirin. No cardiac events such as abrupt closure and myocardial infarction were observed in this trial. Furthermore, no patients who were administered cilostazol experienced headache or any other side effects.

A variety of factors contribute to restenosis after balloon angioplasty. These include inadequate dilatation, chronic elastic recoil, and cellular proliferation [12]. Palmaz-Schatz stent implantation deals with two factors. High-pressure balloon inflations after stenting reduce the problem of inadequate dilatation [13]. Chronic elastic recoil is minimal with Palmaz-Schatz stents [14]. However, a study using intravascular ultrasound showed that cellular proliferation contributes greatly to restenosis after stent implantation [15].

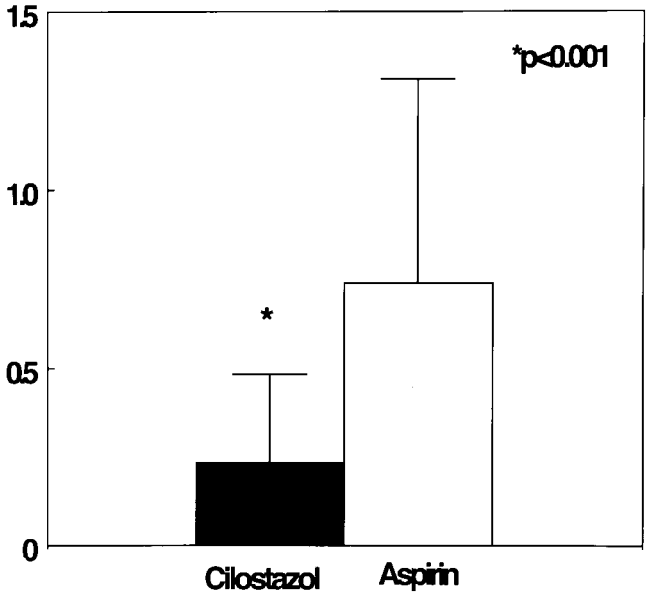

Fig. 2. Loss index (a ratio of late loss and acute gain). Loss index was significantly lower in the cilostazol group than in the aspirin group ($P < 0.001$).

Cilostazol has been shown in animal experiments to inhibit the hyperplasia of stimulated or injured vascular smooth muscle cells after stent implantation. In a placebo-controlled study in dogs, oral administration of cilostazol prevented thrombotic occlusion and intimal hyperplasia after placement of Gianturco Z-stents [9]. This oral dose had been predetermined to achieve 1–2 μg of plasma concentration, which is similar to the plasma concentration reached after 200 mg per day of oral cilostazol in humans.

The effects of cilostazol on intimal proliferation after stent implantation in patients appear to be consistent with those in dogs. Because chronic elastic recoil has been shown to be minimal after Palmaz-Schatz stent implantation, any lumen loss between the stenting and 6-mo follow-up is most likely due to tissue proliferation within the stents. In our study, the acute gain tended to be greater in the cilostazol group than in the aspirin group. Kuntz et al. [11] showed that late loss bears a nearly linear relationship to the acute gain achieved by conventional balloon angioplasty, stenting, and directional coronary atherectomy. In consequence, we would expect the late loss to be greater in the group treated with cilostazol. On the contrary, late loss was smaller in the cilostazol group than in the aspirin group. In earlier studies, late loss after Palmaz-Schatz stent implantation was >0.67–1.22 mm, and loss index was 0.47–0.55 [11,16–18]. These data are comparable to the changes we observed in the group treated with aspirin. The smaller late loss and greater net gain in the cilostazol group, when compared with those of the aspirin group, indicate that the extent of tissue proliferation is smaller in those treated with cilostazol.

Several antiplatelet agents, including aspirin, dipyridamole, and ticlopidine, have been shown to reduce restenosis in the rat carotid model, yet have failed to prevent restenosis when studied in patients [19,20]. More recently, Topol et al. [21] showed that specific platelet IIb/IIIa inhibitors reduce the rate of restenosis after conventional balloon angioplasty in patients with unstable angina, a recent or evolving myocardial infarction, or high-risk angiographic morphology. Further, Schomig et al. [22] showed, in patients with successful Palmaz-Schatz stent implantation, that antiplatelet therapy with ticlopidine results in fewer cardiac events and stent occlusion as compared to conventional anticoagulation therapy with heparin and phenprocoumon.

Limitations

The drug tested was not blinded to either the doctors or the patients in this study. Further, in angiographic analysis, the difference in lumen loss between the cilostazol group and the aspirin group was mathematically significant, but did not reach the criterion of 0.72 mm, which has been reported to be 2 SD of the long-term variation in the measurement of MLDs using a computer-assisted measurement system [23]. Therefore, one cannot exclude the possibility that the absolute change in MLDs does not differ between the cilostazol and aspirin groups. However, the loss index was significantly lower in the cilostazol group, indicating a clear drug-related effect on coronary luminal change after stent implantation.

CONCLUSIONS

In conclusion, cilostazol offers promise in preventing restenosis after Palmaz-Schatz stent implantation. However, a large, double-blinded, multicenter randomized study in a larger population is required to prove its efficacy.

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