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Effects of Antiplatelet Agents on Subacute Thrombosis and Restenosis After Successful Coronary Stenting

A Randomized Comparison of Ticlopidine and Cilostazol

Makoto Sekiguchi, MD; Hiroshi Hoshizaki, MD; Hitoshi Adachi, MD; Shigeru Ohshima, MD; Koichi Taniguchi, MD; Masahiko Kurabayashi, MD*

Background A prospective randomized study compared the preventive effects of ticlopidine plus aspirin therapy versus cilostazol plus aspirin therapy on subacute thrombosis (SAT) and restenosis after coronary stenting.

Methods and Results After successful stenting of 327 coronary lesions in 282 consecutive patients, the patients were randomized to receive ticlopidine (200 mg/day) or cilostazol (200 mg/day). Aspirin (81 mg/day) was administered concomitantly in both groups. SAT occurred in 1 patient in the ticlopidine group (0.7%) and in 8 patients in the cilostazol group (5.6%, p=0.037). Based on follow-up angiography, restenosis occurred in 30 patients (23.3%) in the ticlopidine group and 35 patients (26.9%) in the cilostazol group (NS). The late loss was significantly smaller in the cilostazol group than the ticlopidine group (1.08±0.95 mm vs 0.78±0.93 mm, respectively, p=0.037). No significant differences between the 2 groups were observed with respect to the rates of total death, non-fatal cardiovascular events, or bleeding complications.

Conclusion The ticlopidine group showed significantly less SAT after stenting compared with the cilostazol group. After 6 months of treatment, the inhibition of neointimal proliferation was greater in the cilostazol group than in the ticlopidine group, but the prevention of restenosis was not confirmed. (Circ J 2004; 68: 610–614)

Key Words: Cilostazol; Coronary stenting; In-stent restenosis; Subacute thrombosis; Ticlopidine

Anticipation of platelets is considered to be the main cause of thrombotic occlusion after coronary stenting1,2 and several antiplatelet agents have been shown to be useful for the prevention of subacute thrombosis (SAT). The combination of aspirin and ticlopidine, a selective adenosine diphosphate (ADP) receptor blocker, has prevented SAT after coronary stenting in several randomized studies3–6. Cilostazol, a cyclic adenosine monophosphate phosphodiesterase inhibitor, has also been shown to be a potent antiplatelet agent with antiproliferative properties, suggesting that it should prevent both thrombosis and restenosis after coronary stenting when coadministered with aspirin7–9.

We conducted a prospective randomized study to compare the preventive effects against SAT and restenosis after coronary stenting between ticlopidine plus aspirin and cilostazol plus aspirin.

Study Design

The study included 282 consecutive patients who successfully underwent coronary stenting for the treatment of acute myocardial infarction or angina pectoris. Patients who had already received ticlopidine or cilostazol were excluded. Patients with contraindications to treatment with aspirin, ticlopidine, or cilostazol were also excluded. All patients gave informed consent to participate in this study.

The patients were randomized to the ticlopidine (200 mg/day) plus aspirin (81 mg/day) group or the cilostazol (200 mg/day) plus aspirin (81 mg/day) group. Patients scheduled for elective stenting started on either therapy 2 days before stenting. Those who underwent unplanned stenting because of a suboptimal result after balloon angioplasty or bailout stenting after failed balloon angioplasty received either therapy in the catheterization laboratory. The treatment was continued until follow-up angiography was performed.

Coronary Angiography

The cardiac catheterization and stent implantation were performed according to standard techniques. The technical issues, including the stent type, length, and diameter, and the dilution pressure, were left to the discretion of each attending physician. Coronary angiography was performed before, immediately after and 6 months after stenting.

All of the initial angiographic approaches were also used at follow-up. Images with optimum delineation of the target lesions were selected from among all technically suitable angiograms, and quantitative coronary angiography (QCA) was performed using Integris Quantitative Coronary Analysis (Philips Medical Systems Nederland, The Netherlands) by 2 physicians without any knowledge of the patient's clinical history. The measurements were calibrated using a guide catheter for reference. The reference diameter, minimum luminal diameter (MLD), percent diameter stenosis (%DS) and the gain were determined.

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Division of Cardiology, Gunma Prefectural Cardiovascular Center and *Department of Medicine and Biological Science, Graduate school of Medicine, Gunma University, Maebashi, Japan

Mailing address: Makoto Sekiguchi, MD, Division of Cardiology, Gunma Prefectural Cardiovascular Center, 3-12 Kou, Kamezumicho, Maebashi, Gunma 371-0004, Japan. E-mail: makoto-s@qj8.so-net.ne.jp
The gain was calculated from the difference between the MLD values before and after stenting. The late loss was calculated as the difference between the MLD after stent implantation and the MLD at follow-up, and the loss index was defined as the late loss/gain ratio. Restenosis was defined as 50% or greater stenosis.

**Patient Follow-up**

At each examination, patients underwent clinical evaluation, including assessment of cardiac status, electrocardiographic recording, and assessment of medical compliance. The follow-up angiography was performed whenever there was recurrence of ischemic symptoms and in all patients at 6 months after stenting. When repeat revascularization was required in patients with early recurrence of symptoms, the angiography obtained before the second revascularization procedure was analyzed. In addition, all deaths, all non-fatal cardiovascular events (such as acute myocardial infarction, target lesion revascularization, new lesion revascularization, coronary artery bypass graft surgery), and non-fatal adverse events (including bleeding complications and adverse reactions to drug therapy) were evaluated.

**Endpoints**

The primary endpoints were the incidence of SAT and the incidence of restenosis at 6 months after stenting. SAT was defined as thrombotic stent closure between 24 h and 1 month after coronary stenting. The secondary endpoints were the incidence of all deaths, non-fatal cardiovascular events, and other non-fatal adverse events (including bleeding complications and adverse reactions) up to 6 months after stenting.

**Statistical Analysis**

The data were analyzed on an intention-to-treat basis. The summary statistics (mean values and standard deviations) for the data were calculated and analyzed using the SAS System for Windows (version 6.12). Values of p<0.05 were considered significant.
Results

Baseline Characteristics

There were 138 patients in the ticlopidine group and 144 patients in the cilostazol group. Analyses of the baseline characteristics revealed a significant difference in the percentage of patients with acute myocardial infarction and angina pectoris between the 2 groups. However, there were no significant differences between them for the other characteristics (Table 1). The number of target lesions was 158 in the ticlopidine group and 169 in the cilostazol group. There were no significant differences in the number or extent of target lesions, lesion morphology, or the type or diameter of the stents used (Table 2).

Subacute Thrombosis

SAT occurred in 1 patient in the ticlopidine group (0.7%) and in 8 patients in the cilostazol group (5.6%). All cases of SAT occurred within 1 week after stenting. The incidence of SAT was significantly lower in the ticlopidine group than in the cilostazol group (p=0.037, Fig 1).

Quantitative Coronary Angiography

Restenosis occurred in 30 patients from the ticlopidine group (23.3%) and 35 patients from the cilostazol group (26.9%) during the observation period, with no significant difference between the 2 groups (p=0.567, Fig 2). Table 3 summarizes the evaluation of the target lesions by angiography. The %DS and the MLD before and after stenting showed no significant differences between the 2 groups. During the observation period, the reference diameter was significantly greater in the cilostazol group than in the ticlopidine group (2.98±0.57 mm vs 3.15±0.50 mm, p=0.031). The MLD was also greater in the cilostazol group than in the ticlopidine group, although the difference was not significant (1.87±1.02 mm vs 2.08±1.04 mm, p=0.195). There was no significant difference in the %DS between the ticlopidine and cilostazol groups (37.9% vs 35.0%, p=0.502). The late loss was significantly smaller in the cilostazol group than in the ticlopidine group (1.08±0.95 mm vs 0.78±0.93 mm, p=0.037). The loss index was significantly smaller in the cilostazol group than in the ticlopidine group (0.47±0.47 vs 0.34±0.43, p=0.044).

Table 3  Quantitative Coronary Arteriography

<table>
<thead>
<tr>
<th></th>
<th>Ticlopidine group</th>
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<th>Cilostazol group</th>
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<th>p value (t-test)</th>
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<tr>
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<td>n*</td>
<td>Mean value</td>
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<td>(mean±SD)</td>
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<tr>
<td>Before stent implantation</td>
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<tr>
<td>RD (mm)</td>
<td>158</td>
<td>3.14±0.56</td>
<td>169</td>
<td>3.14±0.55</td>
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<tr>
<td>MLD (mm)</td>
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<td>%DS (%)</td>
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<td>82.6±13.4</td>
<td>169</td>
<td>85.1±14.5</td>
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<td>After stent implantation</td>
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<tr>
<td>RD (mm)</td>
<td>158</td>
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<tr>
<td>MLD (mm)</td>
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<td>169</td>
<td>2.91±0.53</td>
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<tr>
<td>%DS (%)</td>
<td>158</td>
<td>11.4±10.5</td>
<td>169</td>
<td>12.2±10.8</td>
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<td>Gain (mm)</td>
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<td>2.46±0.75</td>
<td>169</td>
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<td>At follow-up</td>
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<td>RD (mm)</td>
<td>86</td>
<td>2.98±0.57</td>
<td>89</td>
<td>3.15±0.50</td>
<td>0.031</td>
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<tr>
<td>MLD (mm)</td>
<td>86</td>
<td>1.87±1.02</td>
<td>89</td>
<td>2.08±1.04</td>
<td>0.195</td>
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<tr>
<td>%DS (%)</td>
<td>86</td>
<td>37.9±27.0</td>
<td>89</td>
<td>35.0±29.7</td>
<td>0.502</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>86</td>
<td>1.08±0.95</td>
<td>89</td>
<td>0.78±0.93</td>
<td>0.037</td>
</tr>
<tr>
<td>Loss index</td>
<td>86</td>
<td>0.47±0.47</td>
<td>89</td>
<td>0.34±0.43</td>
<td>0.044</td>
</tr>
</tbody>
</table>

*Totals based on target lesions. RD, reference diameter; MLD, minimum lumen diameter; %DS, percent diameter stenosis.
Clinical Evaluation

All patients were monitored until follow-up angiography, and all deaths, non-fatal cardiovascular events, and other non-fatal adverse events were investigated (Table 4). There were 2 deaths in the ticlopidine group (1.4%) and 1 (0.7%) in the cilostazol group. Acute myocardial infarction occurred in 3 patients (2.1%) in the cilostazol group. Target lesion revascularization was performed in 11 patients from the ticlopidine group (8.0%) and 14 patients from the cilostazol group (9.7%). New lesions were revascularized for 2 patients in the ticlopidine group (1.4%) and 3 patients in the cilostazol group (2.1%), and coronary artery bypass graft surgery was performed in 1 patient (0.7%) and 2 patients (1.4%), respectively. The incidences of all deaths and non-fatal cardiovascular events were similar in the 2 groups.

Table 5 summarizes the other non-fatal adverse events in each group. Events occurred in 8 patients from the ticlopidine group (5.8%) and 6 patients from the cilostazol group (4.2%, p=0.245). Bleeding complications occurred in 1 patient from the ticlopidine group (0.7%) and 3 patients from the cilostazol group (2.1%). The incidence was slightly higher in the cilostazol group, although the trend was not significant (p=0.623). Hepatic dysfunction was observed in 5 patients from the ticlopidine group (3.6%) and 1 patient from the cilostazol group (1.4%). The incidence was slightly higher in the ticlopidine group, but the trend was not significant (p=0.114). No patient developed serious hepatic dysfunction.

Discussion

The preventive effect against SAT after coronary stenting and the prevention of restenosis up to 6 months after restenosis were studied in the current prospective randomized trial, comparing ticlopidine plus aspirin therapy with cilostazol plus aspirin therapy. In the ticlopidine group, the occurrence of SAT was significantly prevented, compared with that in the cilostazol group. The incidence of restenosis at 6 months was similar in the 2 groups. Therefore, the restenosis-preventing effect that was expected in the cilostazol group was not observed.

Preventive Effect of Ticlopidine on SAT

The significantly greater preventive effect of ticlopidine on the SAT compared with cilostazol may be related to differences in the antithrombotic activity of the 2 agents and the differences in the relative duration of action. Ticlopidine reduces P-selectin expression,11 and inhibits ADP receptors.12 Recent investigation revealed that von Willebrand factor and its interaction with platelet receptor proteins GP Ib and GP IIb/IIIa played an important role in the onset of platelet thrombosis at sites exposed to high shear rates. In particular, inhibition of the P2Y12 receptors was postulated as effective in preventing arterial thrombotic disease.13,14 We speculate that this action of P2Y12 receptor inhibition by ticlopidine contributes to its greater preventive effect on SAT. Cilostazol also inhibits ADP-induced platelet aggregation, but its action is weaker than that of ticlopidine,15 because it is an indirect effect based on the inhibition of cyclic adenosine monophosphate phosphodiesterase and its duration of action is short.16 SAT occurred in 8 patients in the present cilostazol group (5.6%), which is close to the incidence of SAT in the conventional anticoagulation group of the FANTASTIC study.5 Several studies of the preventive effect of ticlopidine and cilostazol against SAT after coronary stenting have been reported. In a Japanese meta-analysis, Isshiki reported that the incidence of SAT was 0.8% in patients receiving ticlopidine and 4.0% in patients with cilostazol (p<0.0001).17 Our results are consistent with his report.

Vascular Effects of Cilostazol

Recent studies reported that cilostazol has a vasodilator action18,19 and inhibits proliferation of aortic smooth muscle cells.20 The QCA findings at follow-up showed that the reference diameter was significantly greater, while the late loss and the loss index were significantly smaller in the cilostazol group than in the ticlopidine group. The greater reference diameter in the cilostazol group was assumed to
be related to its vasodilatory effect, and the significantly smaller late loss and loss index to its antiproliferative effect. However, because the 2 groups showed no significant differences in the MLD or the %DS and no difference in the restenosis rate, it seems that the beneficial effects of cilostazol on the injured vessel were not sufficient to be clinically useful.

A View of Antiplatelet Agents

Because of the small sample size in this study, the superiority of ticlopidine over cilostazol was evident up to 1 month after stent implantation, but it was not clearly demonstrated for longer periods. Therefore, it is not possible to determine from our data how long ticlopidine should be administered after stenting. It has been reported that the adverse reactions, such as serious hepatic dysfunction, granulocytopenia and thrombotic thrombocytopenic purpura, usually appear within 2 months of starting ticlopidine therapy.

In the PCI-CURE study, clopidogrel, a thienopyridine agent similar to ticlopidine, reduced the cardiovascular events significantly as compared with placebo. That is, clopidogrel may be a useful agent to reduce the cardiovascular events than patients in Europe and the United States. Japan. It is necessary to confirm in a large-scale clinical study of clopidogrel whether the same advantages are obtained in Japanese patients, who have a lower incidence of cardiovascular events than patients in Europe and the United States.

Study Limitations

First, this study was a single center study with a relatively small number of patients and there was a significant difference in the indication for revascularization in the 2 groups. Second, this study was not a double-blind trial, despite its prospective, randomized design. Third, intravascular ultrasound was not used, which provides quantitative information, including neointimal volume.

Conclusion

In patients who receive coronary stents, consideration should be given to the use of ticlopidine rather than cilostazol for the prevention of the SAT.

Acknowledgment

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References
