Cilostazol Prevents the Progression of the Symptomatic Intracranial Arterial Stenosis

The Multicenter Double-Blind Placebo-Controlled Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis

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Background and Purpose—Cilostazol, a phosphodiesterase inhibitor, has been reported to reduce restenosis rate after coronary angioplasty and stenting. This study was performed to investigate the effect of cilostazol on the progression of intracranial arterial stenosis (IAS).

Methods—We randomized 135 patients with acute symptomatic stenosis in the M1 segment of middle cerebral artery or the basilar artery to either cilostazol 200 mg per day or placebo for 6 months. Aspirin 100 mg per day was also given to all patients. Patients with potential embolic sources in the heart or extracranial arteries were excluded. IAS was assessed by magnetic resonance angiogram (MRA) and transcranial Doppler (TCD) at the time of recruitment and 6 months later. The primary outcome was the progression of symptomatic IAS on MRA and secondary outcomes were clinical events and progression on TCD.

Results—Thirty-eight patients were prematurely terminated. Dropout rates and reasons for dropouts were similar between the cilostazol and placebo groups. There was no stroke recurrence in either cilostazol or placebo group, but there was 1 death and 2 coronary events in each group. In cilostazol group, 3 (6.7%) of 45 symptomatic IAS progressed and 11 (24.4%) regressed. In placebo group, 15 (28.8%) of symptomatic IAS progressed and 8 (15.4%) regressed. Progression of symptomatic IAS in cilostazol group was significantly lower than that in placebo group (P=0.008).

Conclusion—Our study suggests that symptomatic IAS is a dynamic lesion and cilostazol may prevent its progression. (Stroke. 2005;36:782-786.)

Key words: atherosclerosis ■ cerebrovascular disorders ■ magnetic resonance angiography

Atherosclerotic intracranial arterial stenosis (IAS) is one of the important causes of ischemic stroke, especially in the Asian population.1,2 Despite medical therapy using antiplatelets or anticoagulants, the risk of stroke in patients with IAS remains high.2–4 Surgical management has been attempted but failed to show its benefits.5 Percutaneous transluminal angioplasty may be an alternative management,6 but the efficacy of this procedure still remains to be validated. It also has been known that symptomatic IAS frequently progresses,7,8 which is related to increased risk of vascular events.9 Therefore, prevention of progression may be an alternative management to reduce the risk of stroke in patients with symptomatic stenosis.

Cilostazol, a phosphodiesterase 3 inhibitor, has both antiplatelet function and vasodilating effects,9,10 and has been shown to be effective in the secondary prevention of stroke.11 It also can prevent the occurrence of restenosis after coronary angioplasty and stenting12 and reduce growth of carotid intima-media thickness in diabetic patients.13 Based on these results, it was hypothesized that cilostazol may reduce the progression of IAS and prevent ischemic events. The object of this trial, TOSS (Trial of cilOstazol in Symptomatic intracranial arterial Stenosis), was to investigate the efficacy and safety of cilostazol on prevention of progression against acute symptomatic IAS.

Materials and Methods

Study Design
This study was a multicenter, double-blind, placebo-controlled trial performed in 5 tertiary hospitals in Seoul or neighboring cities in Seoul, Korea.
Participants
We enrolled the patients who: (1) were 35 to 80 years old; (2) had ischemic stroke within 2 weeks from onset; and (3) had symptomatic stenosis in the M1 segment of middle cerebral artery (MCA) or basilar artery (BA). Symptomatic stenosis was defined when there was: (1) stenosis of MCA or BA on magnetic resonance angiography (MRA); and (2) acute ischemic lesions on magnetic resonance imaging (MRI) within the vascular territory of the stenosed artery corresponding to patients’ neurological deficits.

We excluded the patients who had: (1) potential sources of cardioembolism; (2) >50% stenosis of extracranial arteries proximal to the symptomatic intracranial stenosis; (3) known bleeding diatheses or recent major bleeding history; (4) anemia (hemoglobin ≤10 mg/dL) or thrombocytopenia (platelet ≤150 000/mm³); (5) chronic devastating illness; (6) nonatherosclerotic vasculopathy, such as dissection, or moyamoya disease; (7) inadequate transcranial Doppler (TCD) evaluation; (8) occurrence of ischemic stroke during antiplatelets or anticoagulants therapy; and (9) severe stroke (National Institutes of Health stroke scale ≥16 at admission).

Treatment Allocation
Participants were randomly given either cilostazol (100 mg twice daily) or matching placebo, which was supplied by Korea Otsuka Pharmaceutical Company. The randomization order was developed using a computerized random number generator. Aspirin (100 mg once daily) was given to all the participants during the study period.

Evaluation of Stenosis
MRA was primarily used to assess the degree of stenosis, and TCD was additionally performed to support the results based on MRA. MRA was obtained using a 3 dimensional time-of-flight gradient-echo technique for intracranial arteries. On initial assessment, the diagnosis of symptomatic stenosis was made by experienced stroke neurologists and was confirmed by neuroradiologists. TCD evaluations were performed by experienced sonographers according to standardized manual of operations.

Initial MRA and TCD evaluations were performed within 2 weeks after stroke onset. Follow-up evaluations of MRA and TCD were performed 6 months after starting study medication.

Clinical Follow-up
Participants were followed at 1, 3, 5, and 6 months. Laboratory tests were repeated at 1 and 6 months. The amount of remaining study medications was counted at each visit. If the patients did not take study medication >75% (poor compliance) or took other antiplatelet agents, they were dropped out. When serious adverse events developed, participants were also dropped out by the decision of the physician in charge without knowledge of allocation. Stroke or acute coronary syndrome was counted as clinical outcomes, whereas unexplained death was not. Every adverse event was recorded, and its possible association with the study medication was assessed.

Outcome Measurement
The primary outcome was the progression of symptomatic stenosis shown in MRA at 6 months of follow-up. After the completion of follow-up evaluations, the raw data of their MRA were gathered as graphic files, and 3 investigators, who were blinded to the patients’ clinical information, reviewed the data using the same type monitors and single software. The extent of stenosis of 3 arteries (both MCAs and BA) in each patient was classified into 5 grades by consensus: normal, mild (signal reduction ≤50%), moderate (signal reduction ≥50%), severe (focal signal loss with the presence of distal MCA signal), and occlusion. As shown in Figure 1, progression was defined as worsening of stenosis by 1 or more grades on final MRA as compared with the baseline MRA, whereas regression was defined as an improvement of stenosis by 1 or more grade.

The progression of symptomatic stenosis assessed by TCD was used as a secondary outcome. Progression of stenosis on TCD was defined as: (1) the change of waveform to an occlusive pattern; or (2) >20% and >20 cm/s increase in the mean flow velocity on follow-up TCD compared with the baseline value. Regression was defined as: (1) change of waveform from occlusive to stenotic pattern; or (2) >20% and >20 cm/s decrease in the mean flow velocity.

Sample Size Estimate
We assumed that the proportion of progression in symptomatic IAS would be 24% in the placebo group and 12% in the cilostazol group. Based on 0.8 power to detect a significant difference (P=0.05, single-sided), 58 patients should be required for each study group. Assuming a dropout of 15%, the required sample size was 68 in each group. Thus, the initial sample size was determined as 136.

Statistical Analysis
The baseline clinical and radiological characteristics of the 2 treatment groups were compared by unpaired Student t test for continuous variables and by χ² test for categorical variables. The comparison of the results of MRA and those of TCD was made by Mantel–Haenszel χ² test for linear trend. The baseline clinical and radiological characteristics of the incompleters, participants who were prematurely terminated, were also compared with completers, participants who completed the follow-up MRA. A 2-sided P<0.05 was considered statistically significant. SPSS version 10.0 for window software was used for statistical analysis.

Results
From February 2000 to July 2003, 135 patients with symptomatic IAS were enrolled for this trial. Sixty-seven patients were randomly assigned to the cilostazol group and 68 to the placebo group. As shown in Table 1, baseline characteristics and the locations of symptomatic IAS were not different.
between the 2 groups. The proportions of the users of the angiotensin-converting enzyme inhibitors (17.6%) and statins (19.1%) in placebo group were insignificantly larger than those in the cilostazol group (13.4% and 11.9%) (P>0.1).

Clinical Outcome
During the follow-up period, strokes or transient ischemic attacks did not occur, but 2 participants in each group had acute coronary events. Therefore, there were no differences in the clinical outcomes between the 2 groups.

Adverse Events and Dropouts
During follow-up period, headaches (24.4%), gastrointestinal disturbances (16.3%), dizziness (12.6%), respiratory infections (9.6%), skin rash (2.2%), and other adverse events developed. The incidences of the adverse events were not significantly different between the 2 groups, but dizziness and skin rash developed more frequently in the cilostazol group (P<0.05). No serious adverse event was reported in relation to study medication.

Besides 2 clinical outcomes (acute coronary events) in each group, 20 participants (29.9%) were dropped out in the cilostazol group and 14 (20.6%) in the placebo group. One unexplained death occurred in each group. The cause of death in these patients was unknown but was not considered to be caused by vascular events, because clinical and laboratory findings suggesting vascular events were not found. As listed in Table 2, the causes of dropouts were not significantly different between the 2 groups except for the poor compliance (P=0.017).

The Change of Arterial Stenosis
Three assessors blindly reviewed 232 cases (135 baseline and 97 follow-up cases) of MRA and graded the severity of stenosis in 696 arteries (2 MCAs and 1 BA in each case). Inter-rater–weighted \( \kappa \) coefficient of the MCA and BA grading was 0.68 and 0.76, respectively. On the baseline MRA, 259 intracranial arteries (212 MCAs and 47 BAs) were judged as having stenosis, but 10 arteries, which were diagnosed as having symptomatic stenosis at enrollment, were not recognized as being stenosed. The severity of symptomatic IAS was evenly distributed in the 2 treatment groups (Table 1). Follow-up MRA revealed the changes in 187 (symptomatic 97, asymptomatic 90) IAS.

As shown in Table 3, the degree of symptomatic IAS changed in 37 of 97 patients (38.1%). Progression was detected in 3 of 45 patients in the cilostazol group (6.7%) and in 15 of 52 in the placebo group (28.8%), whereas the regression was shown in 11 in the cilostazol group (24.4%) and in 8 patients in the placebo group (15.4%). Thus, the progression was significantly less frequent in the cilostazol group than in the placebo group (P=0.008).

TCD evaluations were completed in 93 patients, and the results were similar; the progression was less frequent in the cilostazol group than in placebo group (P=0.001) (Table 3). The outcomes assessed by MRA and TCD were concordant in 59 of 93 (63.4%) cases, and opposite decisions occurred only in 4 cases (4.3%) (Spearman correlation coefficient=0.32; P=0.002).

As shown in Table 3, the progression rate of asymptomatic stenosis was not different between the 2 treatment groups (P=0.384). The outcome of the symptomatic stenosis was not different according to the severity of stenosis (Table 6).

Characteristics of Incompleters and the Results of Sensitivity Analysis
We compared the clinical and angiographic characteristics of the incompleters to those of completers, who completed follow-up MRA (Table 4). There were no significant differences between the 2 groups in the age, sex, and clinical characteristics except for the coronary artery disease, which was significantly more frequent in the incompleters. The location and severity of the symptomatic IAS were also similar in both groups.
We performed sensitivity analysis to examine the influence of incompleters on the results of this study. Four different assumptions for the progression of symptomatic IAS in the incompleters were applied: the proportion of progression of all incompleters was equal to that of completers: (1) of cilostazol group; (2) of placebo group; (3) of both groups; or (4) the progression of incompleters in the placebo group was equal to that of completers in the cilostazol group, and that of incompleters in the cilostazol group was equal to that of completers in placebo group. As shown in Table 5, the progression rate of symptomatic IAS was significantly lower in the cilostazol/aspirin combination group than in the aspirin monotherapy group. The beneficial effect of cilostazol may be related with its antiatherogenic and antiproliferative action in addition to antiplatelet effects. Large quantities of phosphodiesterase 3 are found in vascular smooth muscle cells, and cilostazol, a phosphodiesterase 3 inhibitor, inhibits smooth muscle cell growth in vitro. Recent studies have revealed that cilostazol has beneficial effects on atherosclerosis related with lipoprotein metabolism. Cilostazol also prevents the generation of apoptosis of endothelial cells caused by remnant lipoprotein particles, which are known to be one of important atherogenic factors. Because cilostazol also has an antiplatelet effect, the combination of this drug with aspirin may increase the risk of bleeding. Fortunately, only 2 minor bleeding complications were observed in the placebo group. Previous clinical trials with aspirin and cilostazol combination have also shown the safety of this regimen.

Our study has several limitations. First, the dropout rate was high enough to threaten the reliability of the results. To overcome the progression of symptomatic IAS and the allocation of treatment disappeared only under the last assumption without the changing in the direction of association.

**Discussion**

We performed this clinical trial to evaluate the outcome of symptomatic IAS and to evaluate the efficacy of cilostazol in this condition. The major findings of our study are: (1) the symptomatic IAS is a dynamic lesion; and (2) aspirin plus cilostazol regimen is tolerable and superior to aspirin monotherapy in the prevention of the progression of symptomatic IAS.

Because digital subtraction angiography was considered invasive, we used MRA to assess the IAS in this study. To augment the reliability of the results, we additionally used TCD. Because there are no validated criteria for the change of IAS with TCD, we arbitrarily defined the change of >20 cm/s and 20% of mean flow velocity as a significant finding. The results obtained by MRA and TCD were similar and concordant. On MRA study, the symptomatic IAS progressed in 29% and regressed in 15% in patients receiving aspirin alone, illustrating that symptomatic IAS is subject to change even at 6 months of follow-up. This dynamic change of symptomatic IAS seems to be consistent with previous observational studies reporting that the progression occurred in 9% to 32.5% and regression occurred in 7.5% to 29%. The progression rate of symptomatic IAS was significantly lower in the cilostazol/aspirin combination group than in the aspirin monotherapy group. The beneficial effect of cilostazol may be related with its antiatherogenic and antiproliferative action in addition to antiplatelet effects. Large quantities of phosphodiesterase 3 are found in vascular smooth muscle cells, and cilostazol, a phosphodiesterase 3 inhibitor, inhibits smooth muscle cell growth in vitro. Recent studies have revealed that cilostazol has beneficial effects on atherosclerosis related with lipoprotein metabolism. Cilostazol also prevents the generation of apoptosis of endothelial cells caused by remnant lipoprotein particles, which are known to be one of important atherogenic factors. Because cilostazol also has an antiplatelet effect, the combination of this drug with aspirin may increase the risk of bleeding. Fortunately, only 2 minor bleeding complications were observed in the placebo group. Previous clinical trials with aspirin and cilostazol combination have also shown the safety of this regimen.

**Table 4.** Comparison of Demographic, Clinical, and Angiographic Characteristics Between the Completers and the Incompleters (Prematurely Terminated Participants)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Completers (n=97)</th>
<th>Incompleters (n=38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>61.9±10.0</td>
<td>63.5±8.8</td>
<td>0.384</td>
</tr>
<tr>
<td>Female (%)</td>
<td>35 (38.8)</td>
<td>18 (47.4)</td>
<td>0.227</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59 (60.8)</td>
<td>19 (50.0)</td>
<td>0.252</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>38 (39.2)</td>
<td>16 (42.1)</td>
<td>0.755</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>45 (46.4)</td>
<td>15 (39.5)</td>
<td>0.467</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>4 (4.2)</td>
<td>7 (18.4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>10 (10.3)</td>
<td>7 (18.4)</td>
<td>0.249</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of symptomatic stenosis</th>
<th>No progression</th>
<th>Progression</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle cerebral artery</td>
<td>82</td>
<td>30</td>
<td>0.437</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>15</td>
<td>8</td>
<td>0.965</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of stenosis</th>
<th>No progression</th>
<th>Progression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7</td>
<td>3</td>
<td>0.010</td>
</tr>
<tr>
<td>Mild</td>
<td>41</td>
<td>16</td>
<td>0.024</td>
</tr>
<tr>
<td>Moderate</td>
<td>29</td>
<td>11</td>
<td>0.017</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
<td>8</td>
<td>0.131</td>
</tr>
</tbody>
</table>

**Table 5.** Sensitivity Analysis: Imaginary Progression Rate of Symptomatic Stenosis in All Recruited Participants (N=135) Based on 4 Assumptions about Progression Rates of Incompleters.

<table>
<thead>
<tr>
<th></th>
<th>Cilostazol (n=67)</th>
<th>Placebo (n=68)</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption 1: Progress Rate of Incompleters</td>
<td>That of Cilostazol Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>5</td>
<td>16</td>
<td>21</td>
<td>0.010</td>
</tr>
<tr>
<td>No progression</td>
<td>62</td>
<td>52</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Assumption 2: Progress Rate of Incompleters</td>
<td>That of Placebo Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>9</td>
<td>20</td>
<td>29</td>
<td>0.024</td>
</tr>
<tr>
<td>No progression</td>
<td>58</td>
<td>48</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Assumption 3: Progress Rate of Incompleters</td>
<td>That of Completers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>7</td>
<td>18</td>
<td>25</td>
<td>0.017</td>
</tr>
<tr>
<td>No progression</td>
<td>60</td>
<td>50</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Assumption 4: Progress Rate of Incompleters</td>
<td>That of Completers of Placebo Group</td>
<td>That of Completers of Cilostazol Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>9</td>
<td>16</td>
<td>25</td>
<td>0.131</td>
</tr>
<tr>
<td>No progression</td>
<td>58</td>
<td>52</td>
<td>110</td>
<td></td>
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P values were calculated by Pearson χ² test.

**Table 6.** The Outcome of the Symptomatic Stenosis According to the Severity of Stenosis on Initial MRA

<table>
<thead>
<tr>
<th></th>
<th>Normal to Mild Stenosis (n=48)</th>
<th>Moderate to Severe Stenosis (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regress (%)</td>
<td>6 (12.5)</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>Stationary (%)</td>
<td>34 (70.8)</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Progress (%)</td>
<td>8 (16.7)</td>
<td>10 (20.4)</td>
</tr>
</tbody>
</table>

P=1.145 by Pearson χ² test.
come this, we performed the sensitivity analysis, which generally supported the favorable outcome of the cilostazol group. The reasons for the dropout were similar between in the cilostazol group and the placebo group. None of the dropouts was considered to be related to serious clinical events, including stroke. However, we cannot completely exclude the possibility that disproportionate dropouts between the 2 groups may have exaggerated the positive effect of cilostazol.

Second, during the study period, no stroke or transient ischemic attacks developed. Therefore, we were not able to examine whether the combination therapy was more effective than aspirin monotherapy in the prevention of clinical events. This was probably caused by the small number of participants, large portion of mild stenosis, and the short duration of follow-up. Further clinical trials focusing on vascular events are required to confirm the clinical efficacy of cilostazol in stroke patients with IAS.

References
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