Cilostazol reduces restenosis after carotid artery stenting

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Background: Although carotid artery stenting (CAS) has been proposed as an alternative to carotid endarterectomy in cerebral revascularization, restenosis remains an unsolved issue. Cilostazol is a unique antiplatelet drug that has vasodilatory effects and inhibits smooth muscle cell proliferation. We investigated whether cilostazol reduces restenosis after CAS.

Methods: A database of 113 consecutive CAS between April 2002 and December 2007 was assessed retrospectively. All patients received aspirin (100mg/day) and another antiplatelet drug such as cilostazol (200mg/day), ticlopidine (200mg/day), or clopidogrel (75mg/day) at least 3 days before CAS. Two antiplatelet drugs were continued for 2 to 3 months after CAS, and reduced to one thereafter. Patients were evaluated at 3 and 6 months and at 6-month intervals thereafter with duplex ultrasonography (US). Angiography was used to confirm when stenosis was suspected as greater than 50% with US.

Results: We were able to follow 97 patients over a 12 month period. The overall combined rate of stroke, myocardial infarction, and death was 3.1% at 30 days, and 4.1% at 1 year. 11 patients (11%) had in-stent recurrent stenosis. Restenosis occurred within 12 months of CAS in 10 patients (9.7%). In-stent restenosis was significantly reduced in the cilostazol (+) group (0% [0/27] vs. 15.7% [11/70], p= .03). Patient characteristics were similar between the cilostazol (+) and cilostazol (-) groups.

Conclusions: Although this study was retrospective and nonrandomized, the results suggest that cilostazol administration improves long-term patency after CAS due to its inhibitory effect on smooth muscle cell growth.

Running Title: Cilostazol reduces restenosis after CAS

Key words: Carotid artery stenting, Cilostazol, In-stent restenosis.

Carotid artery stenting (CAS) is being used widely to treat severe carotid obstructive disease, and it is now accepted as a less invasive technique that provides an alternative for some patients, particularly those with significant comorbidities.[1-5] Although distal embolism decreased with use of the embolization protection device (EPD), up to 10% of patients develop > 50% stenosis as determined by angiography or carotid duplex ultrasound (US) scanning and this problem is not yet solved.[3, 6-8] In some patient subgroup, such as women and the elderly, it approaches 20%.[7]

These series of studies placed aspirin, ticlopidine or clopidogrel as the current standard of antiplatelet drugs. Cilostazol, a cyclic adenosine monophosphate phosphodiesterase inhibitor, has multiple actions including vasodil ation and inhibition of platelet aggregation.[9-11] Cilostazol is widely used as an antiplatelet drug in Japan. Several small trials reported that cilostazol use after endovascular treatment with peripheral artery and coronary artery diseases has a low rate of in-stent restenosis.[12-22] However, it is not known whether a preventive effect of cilostazol on restenosis is similarly recognized after CAS. Accordingly, the present study was undertaken to determine whether cilostazol is effective in preventing restenosis after CAS compared to other antiplatelet drugs.

METHODS

Study design and patient sample.

A retrospective study was conducted of patients who had undergone CAS between April 2002 and December 2007. Carotid duplex US scannings were performed before the stenting procedure, and high grade carotid stenosis was documented in all patients. High-risk patients for CEA with symptomatic carotid stenosis of 50% or greater and asymptomatic carotid stenosis of 80% or greater were considered for the stenting protocol.

Procedural indications, clinical, laboratory, antiplatelet drugs, techniques, treatment outcomes, and postoperative course were analyzed.

Eligibility for CAS was further determined on the basis of criteria established at a consensus conference,[23] including recurrent stenosis after previous CEA; contralateral carotid occlusion; primary lesions in patients with significant medical comorbid conditions, such as coronary artery disease requiring angioplasty or bypass grafting that has not or cannot be revascularized, history of congestive heart failure, current ejection fraction 30% or less (stage III or IV of the New York Heart Association classification), steroid-dependent chronic obstructive pulmonary disease, or measured 1-second forced expiratory volume 30% or less; primary lesion anatomically inaccessible at surgery such as high carotid bifurcation (higher than the C2 level); and primary lesion with previous ipsilateral cervical radiation therapy.

Carotid artery stenting procedures (n=113) were performed in 106 patients over this period. We were able to follow 97 patients over 12 months. These included 83 men and 14 women with the mean age being 69.9±7.2 years. 61 patients (62.9%) had symptomatic stenosis; 36 patients (37.1%) had asymptomatic lesions. Indications for carotid artery stenting included recurrent stenosis after previous CEA (n=5, 5.1%), high-risk cardiac comobidity (n=26, 26.8%), high-risk pulmonary comobidity (n=1, 1.0%), high carotid bifurcation (n=30, 30.9%) and previous ipsilateral cervical radiation therapy (n=8, 8.2%). Clinical characteristics are presented in Table 1.

Carotid artery stenting protocol.

All patients were examined prior to each procedure to ascertain neurological function by independent neurologist; duplex US scanning was also performed in all cases. Patients treated electively received aspirin (100mg/d) and another antiplatelet agent such as clopidogrel (75mg/d), ticlopidine (200mg/d), or cilostazol (200mg/d) for at least 3

days before the intervention. Patients electively received aspirin, and thienopyridine (ticlopidine or clopidogrel). In Japan, because Clopidogrel was approved by the pharmaceutical affairs from December, 2006, patients received ticlopidine before then, and clopidogrel was added since December 2006. In cases of the patients with peripheral artery disease or coronary artery disease, cilostazol and/or thienopyridine was added before carotid artery stenting. This combination of antiplatelet drugs was continued from the formula of the cardiovascular medicine. Standard monitoring techniques were employed, including intra-arterial pressure monitoring, oximetry, and continuous electrocardiography. During the procedure, the patient's neurological status was continuously monitored via verbal command.

Standard retrograde access was achieved in the common femoral artery under local anesthesia with 1% lidocaine. An 8F vascular sheath was inserted. Heparin was administered to achieve an activated clotting time of over 300 seconds. An 8F guiding catheter was navigated into the common carotid artery. Carotid angiogram and intracranial injections were performed. A 0.018-inch guidewire system with EPD was then manipulated to cross the internal carotid lesion. For the patients with high-grade stenosis which was nearly occluded or with thrombosis, procedures were performed using the reversed-flow system. After the activation of the embolic system, a coaxial angioplasty balloon was used to predilate the carotid lesion if necessary. Next, a self-expanding carotid stent was deployed across the internal carotid stenosis. Post-dilatation was performed if necessary. On completion, ipsilateral cervical and intracranial carotid angiography was performed to assess technical success and to exclude distal cerebral embolization.

Patients were monitored in an intensive care unit overnight after the procedure, and

were discharged 3 or 4 days after the procedure. Postprocedure clinical examination and duplex US scanning were performed before discharge, to confirm stent patency and position. One antiplatelet drug was prescribed to be taken for life and another one to be terminated after 2 or 3 months. Aspirin was prescribed to be taken for life basically. In cases of the patients with peripheral artery disease or coronary artery disease, cilostazol and/or thienopyridine was added before carotid artery stenting. This combination of antiplatelet drugs was continued from the formula of the cardiovascular medicine. After CAS, this combination was continued for life.

Follow-up protocol and criteria for restenosis assessment.

All patients were followed at the hospital's outpatient clinic at 1, 3, 6, 9 and 12 months after the procedure and every 6 months thereafter. During these routine postoperative visits, the surgeon and independent neurologist examined each patient, and carotid duplex US scans were performed at 3 and 6 months and at 6-month intervals thereafter. The velocity criteria used to evaluate carotid artery stenosis were modifications of the Japanese Academy of Neurosonology Guidelines for Neurosonology and were validated in our hospital. Peak systolic velocity greater than 150 cm/s correlated with greater than 50% stenosis.[24] Additionally, luminal reductions on grayscale images and color flow disturbances were further evaluated. In-stent restenosis, identified by US scanning, was further verified by carotid angiography, and stenosis was measured geometrically on the basis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[25] When more than 50% restenosis was recognized, carotid angioplasty and possible stenting were subsequently performed.

Statistical analysis.

Clinical variables that may be associated with restenosis after CAS were analyzed. Data

are shown as mean ± standard deviation (SD). The unpaired t-test was used to compare continuous variables between the groups. The chi-square test or Fisher's exact test was used to compare ratios. Statistical significance was defined as a $p < 0.05$.

RESULTS

Thirty-day and one-year outcome of carotid artery stenting.

The lesion was accessed and the procedure performed successfully in all cases, for a technical success rate of 100%. Mean stenosis treated was 82.9±9.5%, and post-treatment mean residual stenosis was 5.2±0.5%. Wallstents (Boston Scientific, Natick MA, USA) were deployed in 71 procedures (73.2%), Precise (Cordis, Miami FL, USA) in 8 procedures (8.2%), Protage (eV3, Plymouth, Minn, USA) in 2 procedures (2.1%), Xpert (Abbott Vascular, Redwood City, Calif, USA) in 1 procedure (1.0%), and SMARTeR stent (Cordis) in 15 procedures (15.5%). All stenting procedures were performed by using EPD, including the PercuSurge Guardwire device (Medtronic, Minneapolis MN, USA; n=82; 84.5%), AngioGuard XP (Cordis; n=7; 7.2%), and reversed-flow system (n=7; 7.2%).

Overall 30-day stroke, myocardial infarction, and death rate was 3.1% (n=3). Each of the three strokes was minor (two ipsilateral minor strokes and one contralateral stroke). Post operative duplex US scanning was performed within a week after CAS. There were no in-stent restenosis, carotid dissections, or thromboses in all patients. During one-year follow-up, myocardial infarction was noted in one patient. Over all one-year outcome for stroke, myocardial infarction, and death was 4.1%.

Long-term follow-up and in-stent restenosis.

During follow-up of 12 to 67 months (mean, 28.6±13.3 months), 9 patients were lost in the follow-up. In-stent restenosis confirmed by duplex US scanning and

angiography was detected in 11 (11.3%) of 97 carotid arteries. Recurrent stenosis occurred within 5 to 16 months (mean, 8.9±3.0 months). Mean restenosis was 55.5%±7.2%, and mean peak systolic velocity was 200.8±75.1 cm/s. None of the patients showed symptoms of recurrent stenosis. There were ten men and one woman with mean an age of 69.3±16.2 years. In comparing patient characteristics, clinical symptoms, CAS indications, CAS devices, and CAS technique between the patients with in-stent restenosis and without in-stent restenosis, no significant difference was noted (Table 2).

Two patients did not want re-treatment and were followed up with serial clinical evaluation and duplex US scanning at 3-month to 6-month intervals. Nine of eleven patients underwent endovascular repeat intervention; five of which were repeat balloon angioplasty with four being repeat angioplasty and secondary stenting. Technical successes were achieved in all patients, and the mean carotid artery stenosis decreased from 54.6% to 11% after reintervention. No procedural related complications were noted after in-stent restenosis intervention. All patients who underwent reintervention have remained rec urrence-free during follow-up periods (20.6 month median).

Post-CAS antiplatelet therapy and in-stent restenosis.

Antiplatelet drugs that were continued for 1-year after CAS are presented in table 3. The combinations of antiplatelet agents were as follows (aspirin n=28, ticlopidine n=3, clopidogrel n=10, cilostazol n=1, aspirin + ticlopidine n=23, aspirin + clopidogrel n=6, aspirin + cilostazol n=19, cilostazol + clopidogrel n=3, aspirin + ticlopidine + cilostazol n=1, aspirin + clopidogrel + cilostazol n=3). No significant differences were noted in overall 30-day and 1-year stroke, myocardial infarction, and death among each drug group. Among the cilostazol (+)

group, there were significantly fewer incidences of restenosis compared to patients without cilostazol (0% vs. 15.7%, p= .03). The restenosis rate was significantly higher in patients who took ticlopidine compared to patients without ticlopidine (25.9% vs. 5.7%, p= .01). Patient, lesion characteristics, and CAS technique did not differ between the cilostazol (+) and cilostazol (-) groups. Use of additional drugs was similar between the groups, except that ticlopidine was used more frequently in the cilostazol (-) group than in the cilostazol (+) group.

DISCUSSION

The incidence of postprocedural in-stent restenosis ranges from 1% to 50% in published reports.[1, 3, 26-28] The reported rate of in-stent restenosis depends on the definition of recurrent stenosis, duration of follow-up, and the methods of diagnosis. Although most of these reports were based on short follow-up periods, several authors more recently presented findings after periods of longer follow-up. Setacci et al[29] reported a 3.6% incidence of high-grade restenosis (> 80%) over a 21 month follow-up period with more than 372 carotid stents. Similarly, Chakhtoura et al[26] reported an 8% high-grade restenosis rate during their 18 month follow-up of 50 carotid stent procedures. Our study, likewise, demonstrated an 11.3% moderate-grade (> 50%) in-stent restenosis rate during a mean 28.6 month follow-up period.

Cilostazol, a phosphodiesterase 3 inhibitor has antiplatelet action and vasodilatory effects and inhibits smooth muscle cell proliferation.[10, 11, 31, 32] It has been reported that cilostazol increases the cyclic adenosine monophosphate phosphodiesterase level in vascular smooth muscle cells, resulting in upregulation of the antioncogenes p53 and p21 and hepatocyte growth factor.[33] Because the increase in p53 protein blocks cell cycle progression and induces apoptosis in vascular smooth

muscle cells, these mechanisms have an antiproliferative effect .[34] Furthermore, hepatocyte growth factor stimulates re-endothelization after vascular injury, inhibits abnormal vascular smooth muscle cell growth, and improves endothelial function.[35] Because one of the major causes of recurrent stenosis after CAS is neointimal hyperplasia, these actions may possibly explain the beneficial effect of cilostazol on reducing the in-stent restenosis rate. Cilostazol also inhibits P-selectin-mediated leukocyte activation, platelet-leukocyte interaction, and subsequent Mac-I-mediated leukocyte activation.[36] Because inhibition of these actions is thought to reduce neointimal thickening after vascular injury, this mechanism may be also be important in the reduction of restenosis after CAS.

Earlier studies have indicated that cilostazol improves symptoms and increases walking distance in patients with peripheral artery disease with intermittent claudication.[12] Recently, studies have shown that cilostazol reduces restenosis and target lesion revascularization after percutaneous transluminal angioplasty in patients with peripheral artery disease.[13-15] Consequently, cilostazol is a class 1 drug for patients with peripheral artery disease according to American Heart Association guidelines.[37] Furthermore, several studies have shown that cilostazol has the potential to reduce restenosis compared with aspirin after balloon angioplasty, stent implantation, and directional coronary atherectomy.[16-20] Douglas JS et al[12] reported that cilostazol was effective on restenosis after coronary artery stenting when compared to placebo-treated patients. Tanabe et al[21] reported on cilostazol's effect on restenosis after coronary angioplasty and stenting in comparison to coronary artery stenting with ticlopidine.

In the study presented here, cilostazol was as effective as other antiplatelet drugs in preventing periprocedual and 1-year complications after CAS, as evidenced by the lack of any significant differences in vascular events observed at the 30-day and 1-year follow-ups. Furthermore, cilostazol showed more effectiveness in reducing restenosis after stent implantation than the other antiplatelet drugs. The inhibitory effect of cilostazol on restenosis may not be due to its antiplatelet effects but is possibly due to its direct inhibition of smooth muscle cell growth.

This study was a nonrandomized, retrospective at a single center trial, and there were few numbers. A large-scale, prospective, multicenter study should be undertaken to verify these preliminary conclusion.

CONCLUSION

Cilostazol may have the potential to reduce the rate of restenosis after CAS due to its inhibitory effect on smooth muscle cell growth.

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Table 1: Patient characteristics

	Total (n=97)
Age (y) (mean ± SD)	69.6±7.2
Male sex, n (%)	83 (85.6)
Type of lesion	
Asymptomatic carotid stenosis, n (%)	36 (37.1)
Symptomatic carotid stenosis, n (%)	61 (62.9)
Stroke, n (%)	38 (39.2)
Transient ischemic attack, n (%)	16 (16.5)
Amaurosis fugax, n (%)	7 (7.2)
Severity of stenosis (%) (mean ± SD)	82.9±9.5
Comorbidities	
Coronary artery disease, n (%)	32 (33.0)
History of myocardial infarction, n (%)	18 (18.6)
Smoking, n (%)	70 (72.2)
Hypertension, n (%)	78 (80.4)
Diabetes, n (%)	29 (29.9)
Chronic obstructive pulmonary disease, n (%)	1 (1.0)
Hypercholesterolemia, n (%)	49 (50.5)
Renal insufficiency, n (%)	7 (7.2)
Peripheral artery disease, n (%)	8 (8.2)
CAS indications	
High-risk cardiac comobidity, n (%)	26 (26.8)
High carotid bifurcation, n (%)	30 (30.9)
High-risk pulmonary comobidity, n (%)	1 (1.0)
History of neck irradiation, n (%)	8 (8.2)
Post CEA stenosis, n (%)	5 (5.1)

CAS, carotid artery stenting; CEA, carotid endarterectomy.

Table 2: Comparison of patient characteristics, clinical symptoms, CAS indications, CAS devices, and CAS technique between the patients with in-stent restenosis and without in-stent restenosis.

	No ISR (n=86)	ISR (≧50%) (n=11)	P value
Age (y) (mean ± SD)	69.7±7.2	69.3±7.9	NS
Male sex (%)	84.8	90.1	NS
Type of lesion			
Asymptomatic carotid stenosis (%)	38.4	27.3	NS
Symptomatic carotid stenosis (%)	61.6	72.7	NS
Stroke (%)	38.4	45.5	NS
Transient ischemic attack (%)	16.2	18.1	NS
Amaurosis fugax (%)	7.0	9.1	NS
Severity of stenosis (%) (mean ± SD)	82.5±9.9	85.8±5.2	NS
Comorbidities			
Coronary artery disease (%)	32.5	36.4	NS
History of myocardial infarction (%)	18.6	18.2	NS
Smoking (%)	70.9	81.8	NS
Hypertension (%)	82.6	63.6	NS
Diabetes (%)	30.2	27.3	NS
Chronic obstructive pulmonary disease (%)	1.2	0	NS
Hypercholesterolemia (%)	51.2	45.5	NS
Renal insufficiency (%)	8.1	0	NS
Peripheral artery disease (%)	8.1	9.1	NS
CAS indications			
High-risk cardiac comobidity (%)	26.7	27.3	NS
High carotid bifurcation (%)	30.2	36.4	NS
High-risk pulmonary comobidity (%)	1.2	0	NS
History of neck irradiation	8.1	9.1	NS
Post CEA stenosis	5.8	0	NS
Stents			
Wallstent (%)	74.4	63.6	NS
Precise (%)	8.1	9.1	NS
SMARTeR (%)	14.0	27.2	NS
Xpert (%)	1.2	0	NS
Protage (%)	2.3	0	NS
EPD			
PercuSurge Guardwire device (%)	83.7	90.9	NS
AngioGuard (%)	7.0	9.1	NS
Navi balloon (%)	1.2	0	NS
Reversed-flow system (%)	8.1	0	NS
Pre-balloon dilatation (%)	97.7	100	NS
Post-balloon dilatation (%)	80.2	72.7	NS
Post-treatment residual stenosis (%) (mean ± SD)	4.8±5.2	8.9±8.0	NS

ISR, in-stent restenosis; CAS, carotid artery stenting; NS, not significant; CEA, carotid endarterectomy, EPD; embolization protection device

Table 3. Antiplatelet drugs used in 97 patients after CAS for a year.

	N	Overall 30-day stroke, myocardial infarction, and death (n=3)	Overall 1-year stroke, myocardial infarction, and death (n=4)	restenosis (n=11)
Aspirin (+)	80	2 (2.5%)	3 (3.8%)	8 (10.0%)
Aspirin (-)	17	1 (5.9%)	1 (5.9%)	3 (17.6%)
Cilostazol (+)	27	1 (3.7%)	1 (3.7%)	0 (0%) *
Cilostazol (-)	70	2 (2.9%)	3 (4.3%)	11 (15.7%)
Ticlopidine (+)	27	0 (0%)	1 (3.7%)	7 (25.9%) **
Ticlopidine (-)	70	3 (4.3%)	3 (4.3%)	4 (5.7%)
Clopidogrel (+)	22	2 (9.1%)	2 (9.1%)	3 (13.6%)
Clopidogrel (-)	75	1 (1.3%)	2 (2.7%)	8 (10.7%)

*p= .03; **p= .01