ORIGINAL RESEARCH

Effect of Cilostazol in Preventing Restenosis after Carotid Artery Stenting Using the Carotid Wallstent: A Multicenter Retrospective Study

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BACKGROUND AND PURPOSE: Restenosis after CAS is a postoperative problem, with a reported frequency of approximately 2%–8%. However differences in stent design, procedure, and the antiplatelet agent appear to affect the incidence of restenosis. We assessed the frequency of restenosis and the effect of the antiplatelet agent CLZ in preventing restenosis after CAS by the standard procedure using the CWS.

MATERIALS AND METHODS: Between May 2010 and October 2011, 62 lesions in 60 consecutive patients underwent CAS using the CWS at 4 medical institutions, and all patients were followed clinically and assessed by sonography, 3D-CTA, or angiography at 3 and 6 months postoperatively. Restenosis was defined as ≥50% stenosis. The incidence of restenosis and the variation in the incidence of restenosis by the difference in type of antiplatelet agent between the CLZ group ($n = 30$; aspirin, 100 mg, and CLZ, 200 mg) and the non-CLZ group ($n = 32$; aspirin, 100 mg, and clopidogrel, 75 mg [$n = 29$]; or ticlopidine, 100 mg [$n = 2$] or 200 mg [$n = 1$]) were retrospectively investigated. Two antiplatelet agents were given starting 1 week preoperatively until at least 3 months postoperatively.

RESULTS: Restenosis occurred in 5 patients (8.3%), but all were cases of asymptomatic lesions in the follow-up period. All 5 patients with restenosis were in the non-CLZ group, with no cases of restenosis in the CLZ group; the difference was significant ($P = .0239$).

CONCLUSIONS: The restenosis rate after CAS by using the CWS was 8.3%. CLZ was associated with significant inhibition of restenosis.

ABBREVIATIONS: CAS = carotid artery stenting; CEA = carotid endarterectomy; CLZ = cilostazol; CWS = Carotid Wallstent; EPC = endothelial precursor cell; EPD = embolic protection device; PTA = percutaneous balloon angioplasty

CAS is becoming an alternative to CEA.[1] However, restenosis is a postoperative problem, with a reported frequency of 2.27%–8%,[2-5] though those figures include several stents and stents that are no longer used. Stents for the carotid artery are now also being developed. These stents come primarily in the form of self-expanding open-cell and closed-cell stents, with differences in stent design and radial force. It is currently recommended that poststent balloon dilation should be performed conservatively in the consensus standard CAS technique.[6] Differences in stent design and procedure appear to affect the incidence of stenosis, and the antiplatelet agent CLZ has also been reported to inhibit restenosis.[7] The aim of this study was to investigate the frequency of restenosis and the effect of CLZ in preventing such restenosis after CAS by the standard procedure using the CWS (Boston Scientific, Natick, Massachusetts).

Received February 8, 2012; accepted after revision February 28.

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http://dx.doi.org/10.3174/ajnr.A3127

Materials and Methods

During 18 months between May 2010 and October 2011, 62 lesions in 60 consecutive patients with common or internal carotid artery stenosis underwent elective CAS by using the CWS at 4 medical institutions (Ishinkai Yao General Hospital, Higashiosaka City Hospital, Heisei Memorial Hospital, Nara Medical University Hospital) with written informed consent. The study included 60 patients (54 men, 6 women; age range, 51–97 years; mean, 72.9 years) and 62 lesions (26 symptomatic lesions of ≥50%, 36 asymptomatic lesions of ≥80%; mean stenosis [NASCET method]),[8] 81.5%; all arteriosclerotic stenosis). All cases of CAS were successful, and perioperative complications in cases of CAS consisted only of minor stroke in 2 patients (3.3%), both of which resolved within 30 days postoperatively. All patients were monitored with time on the basis of clinical and imaging findings.

CAS Procedure

CAS was performed in all patients by the standard procedure on which consensus has been obtained in the United States.[6] The EPD (FilterWire EZ; Boston Scientific) was first introduced, the lesion was then predilated with a balloon 3 or 4 mm in diameter, the stent was placed, conservative postdilation was performed, and the EPD was then removed. Conservative postdilation means that postdilation was performed by using a PTA balloon with a diameter no greater than approximately 80% of the normal luminal diameter somewhat distal to the stenosis as determined by intravascular sonography (postdilation balloon diameter, 4–6 mm; mean, 4.75 mm). The minimum lesion diameter after the procedure was

2.85–6.4 mm (mean, 3.68 mm). The procedure was completed with as much as 30%–40% residual stenosis on angiography.

Antiplatelet Medication

All patients were given at least 2 antiplatelet agents starting 1 week preoperatively. The treatment was continued for at least 3 months postoperatively. The antiplatelet agents were aspirin (100 mg) and ticlopidine (100 mg) in 2 patients, ticlopidine (200 mg) in 1 patient, aspirin and clopidogrel (75 mg) for 29 lesions in 28 patients, and aspirin and CLZ (200 mg) for 30 lesions in 29 patients. The agents were administered while previous medication was continued without modification. The administration of CLZ was prioritized in cases with comorbid arteriosclerosis obliterans and was otherwise randomized.

Analysis

The frequency of restenosis during follow-up and variations in the incidence of restenosis by the difference in type of antiplatelet agent (the CLZ group and the non-CLZ group) were retrospectively analyzed. Restenosis, defined as ≥50% stenosis, was assessed by sonography, 3D-CTA, or angiography 3 and 6 months postoperatively. The χ^2 test was used for comparison of proportions, and the unpaired *t* test, for comparison of means in clinical characteristics and findings on procedures between the both groups. Data are shown as mean ± SD. Statistical significance was defined as $P < .05$.

Results

Restenosis occurred in 5 patients (8.3%), all within 6 months (within 3 months in 2 patients and within 6 months in 3 patients). Three patients (5.0%) were retreated (PTA in 1 patient and PTA following open-cell stent placement in 2 patients) because of 80% or greater restenosis in asymptomatic lesions. No ipsilateral stroke was observed during follow-up (3.5–20.5 months; median, 13.0 months).

All 5 cases of restenosis were in the non-CLZ group: Four were from the clopidogrel group, and 1 was from the ticlopidine group. The restenosis rate in the non-CLZ group was 15.6% (5/32), while the restenosis rate in the CLZ group was 0% (0/30); the difference was statistically significant ($P = .0239$). Comorbidities of the study group included hypertension in 50 (83.3%), hypercholesterolemia in 50 (83.3%), diabetes mellitus in 29 (48.3%), and being a smoker in 25 (41.7%). There were no statistically significant differences in parameters other than CLZ treatment between the 2 groups. Parameters (the CLZ group versus the non-CLZ group) were the following: age (73.1 ± 9.2 years versus 72.7 ± 6.9 years); sex (male 27, female 2 versus male 27, female 4); type of lesion (symptomatic: 15 versus 11; asymptomatic: 15 versus 21); length of lesion (short, ≤2 cm: 9 versus 16; long, >2 cm: 21 versus 16); comorbidities such as hypertension (24 versus 27); hypercholesterolemia (13 versus 18); diabetes mellitus (12 versus 9); being a smoker (15 versus 10); severity of stenosis (82.47 ± 9.72% versus 80.37 ± 11.24%); postballoon diameter (4.608 ± 0.548 mm versus 4.828 ± 0.617 mm); stent diameter (6 mm: 0 versus 2; 8 mm: 19 versus 17; 10 mm: 11 versus 13); residual stenosis postprocedure (25.00 ± 12.3% versus 20.97 ± 10.82%); and minimum lesion diameter postprocedure (3.63 ± 0.46 mm versus 3.70 ± 0.67 mm).

Discussion

CLZ is an antiplatelet agent with clinical vasodilating action, but it has been reported to inhibit smooth-muscle cell proliferation and to act on endothelial cells.[9,10] Kubota et al[11] first reported that CLZ prevented intimal hyperplasia after stent placement in an experimental study. In this study in dogs, self-expanding Z-stents were placed in the iliac arteries to compare a group given CLZ orally and an unmedicated group. The thickness of the neointima was significantly thinner in the CLZ group than in the unmedicated group at 24 weeks. The authors concluded that oral administration of CLZ was an effective method of preventing thrombotic occlusion and intimal hyperplasia after stent placement. However, the distinct mechanism involved in specifically preventing restenosis is not yet known. In a report by Kawabe-Yako et al[12] in 2011, a carotid balloon injury model (in rats) was used to compare a group given CLZ mixed in feed starting 2 weeks before intimal injury and a group fed a normal diet. Comparison revealed accelerated re-endothelialization 2 weeks after carotid intimal injury in the CLZ group, resulting in significant inhibition of neointimal formation after 4 weeks compared with the control group. The proposed mechanism was stated as follows: CLZ increases the number of bone marrow–derived EPCs and promotes EPC recruitment to sites of arterial injury, thereby inhibiting neointimal formation by promoting re-endothelialization with EPCs as well as existing vascular endothelial cells.

The inhibitory effect of CLZ on poststenting restenosis clinically has been reported in arteriosclerotic stenotic diseases throughout the body (carotid artery, coronary artery, and femoropopliteal artery). Takigawa et al[7] reported a comparison of a group using CLZ (27 patients) and a group not using CLZ (70 patients) after CAS; the restenosis rate was 15.7% in the non-CLZ group with no restenosis in the CLZ group, showing a significantly greater reduction in restenosis in the CLZ group. Several different kinds of stents were used in this study. Closed-cell stents (Wallstent; Boston Scientific) were used more often (in approximately 70%), but open-cell stents were also used. In a report by Tanabe et al[13] involving a comparison of 112 lesions after coronary angioplasty (aspirin, 81 mg [64 lesions]; CLZ, 200 mg [48 lesions]) and 118 lesions after coronary artery stent placement (aspirin, 81 mg, and CLZ, 200 mg [63 lesions]; aspirin, 243 mg; and ticlopidine, 200 mg [55 lesions]), the incidence of restenosis after coronary angioplasty was 12.5% in the CLZ group and 43.8% in the aspirin group, and the incidence after coronary artery stent placement was 14.3% in the CLZ group and 32.7% in the ticlopidine group. There was better inhibition of restenosis by CLZ in both.

Douglas et al[14] reported a randomized double-blind placebo-controlled trial in 705 subjects after coronary artery stent placement; there was significantly inhibited restenosis in the CLZ group, with a restenosis rate of 22.0% in the CLZ group and a restenosis rate of 34.5% in the placebo group. Iida et al[15] reported that in a prospective randomized study on vasodilation and stent placement procedures for femoropopliteal lesions (characterized by high rates of restenosis), a comparison of 63 lesions treated with aspirin and CLZ and 64 lesions treated with aspirin and ticlopidine showed that the patency rates after 1, 2, and 3 years were 87%, 82%, and 73%, respec-

tively, in the CLZ group, and 65%, 60%, and 51%, respectively, in the ticlopidine group, with significant inhibition of restenosis by CLZ.

The incidence of restenosis in CAS reportedly ranges from 2.27% to 8%, but differences in stent design are associated with differences in incidence. The reported incidence was 3.8% in studies in which open-cell stents were used in 91% of cases,[4] 8% in studies in which closed-cell stents were used in 98% of cases,[3] and 4.85% in studies in which open-cell stents were used in 65% and closed-cell stents were used in 35% of cases.[5] Open-cell stents appear to be associated with a lower incidence of restenosis than closed-cell stents. This may be the result of the stent structure. Closed-cell stents have weaker radial force and somewhat poorer wall apposition than open-cell stents. In addition, postoperative stent shortening often occurs with the Wallstent and the CWS, which are both closed-cell stents. Restenosis has reportedly occurred when stents deployed in stenotic sites shifted as a result of stent shortening.[16] In the present study, no case of restenosis was found to involve shortening.

The incidence of restenosis was 8.3% with the closed-cell CWS used in all cases in the present study; in particular, the rate was 16.1% in the non-CLZ group. The long-term results in the BEACH study,[17] in which the same CWS as in the present study was used, showed a 2.7% (12/447) incidence of ipsilateral neurologic events from 31 days to 1 year after CAS, an 8.9% (40 of 447) restenosis (≥70% stenosis) rate, and a 4.7% (20 of 425) retreatment rate. It is believed that the incidence of restenosis, if defined as at least 50% stenosis, would be even higher and would presumably be as high as in the present study. Lin et al[18] reported that 97%, 94%, 89%, and 85% of 380 patients in whom the CWS was used were stroke-free for 1, 2, 3, and 4 years, respectively, with restenosis (≥60% stenosis) rates of 3%, 6%, 8%, and 10%, respectively, indicating that the incidences of restenosis and stroke increased with time.

Meanwhile, using open-cell stents, the results of the SAPPHIRE study[19] on the use of the Precise self-expanding stent (Cordis, Miami Lakes, Florida) showed a 1.3% incidence of ipsilateral stroke from 31 days to 1 year after CAS and a 0.6% retreatment rate (1/167). Although the incidence of restenosis was not reported, the retreatment rate of 0.6% suggests that the restenosis rate may be lower when carotid open-cell stents are used than when carotid closed-cell stents are used. Jansen et al[20] stated that on the basis of the results of a trial comparing CEA and CAS in conventional-risk patients (CEA for symptomatic stenosis ≥60%; SPACE trial) reported in 2004, ipsilateral stroke and stroke death were significantly lower in patients treated with closed-cell stents (closed-cell stents, 5.5% [24/435]; open-cell stents, 11.0% [14/127]). Analyzed by type of stent, the incidence of ipsilateral stroke and stroke death was lowest with the CWS (5.5%, 24/436), followed by the Acculink stent (Guidant, St Paul, Minnesota) at 9.8% (9/92) and the Precise self-expanding stent at 14.3% (5/35).

Takayama et al[21] reported that stroke occurred in 1 case (6.7%) during the initial use of the open-cell Precise self-expanding stent in 15 subjects after CAS, with a positive rate of 53.3% on postoperative DWI. On the other hand, favorable results were reported with the initial use of the CWS in 15 cases after CAS, in which not a single case of TIA, stroke, or death was found, with a positive rate of 6.7% on DWI.[22] In a review of 1363 cases in 32 studies, Schnaudigel et al[23] also reported that the incidence of ipsilateral ischemic lesions treated by CAS, as determined on DWI, was 31% with closed-cell stents and 51% with open-cell stents, revealing a significantly lower incidence with closed-cell stents. It appears that closed-cell stents are a better option for lowering the incidence of perioperative stroke in cases of CAS.

In the United States, the use of 2 agents (aspirin, 81–325 mg; and clopidogrel, 75 mg) is recommended for at least 1 month as the perioperative antiplatelet treatment regimen in cases of CAS.[6] In Japan, however, the recommended use of 2 agents includes not only aspirin (100 mg) and clopidogrel (75 mg) but also aspirin (100 mg) and CLZ (200 mg). In addition, life-long monotherapy with aspirin is recommended in both the United States and Japan when patients are switched from 2-agent treatment to monotherapy. However, in the prospective study Cilostazol for Prevention of Secondary Stroke (CSPS 2),[24] which compared aspirin, 81 mg, and CLZ, 200 mg, in preventing cerebral infarction in 2672 Japanese patients, the annual stroke incidence was 2.76% in the CLZ group and 3.71% in the aspirin group, indicating significant prevention of stroke in the CLZ group. In addition, the incidence of hemorrhagic events was 1.2% in the aspirin group versus 0.036% in the CLZ group, demonstrating the superiority of CLZ. Recently Kato et al[25] reported that CLZ also significantly prevented progression of contralateral asymptomatic carotid artery stenosis in 95 patients treated by CAS. It might be worthwhile to recommend the life-long use of CLZ rather than aspirin as the antiplatelet agent after CAS.

Although this study has the limitation of a nonrandomized, nonprospective, noncomparative study at 4 centers with a rather small sample size, the effectiveness of CLZ for preventing restenosis after CAS was suggested. For further evaluation, a prospective comparative study involving a greater number of patients may be needed in the future to properly assess these initial results. A prospective study on the use of open-cell stents with the standard procedure may also be needed to assess the effect of CLZ in preventing restenosis in all cases of CAS.

Conclusions

The restenosis rate was 8.3% after CAS with the CWS by the standard procedure. There was no significant restenosis in the CLZ group by using the CWS. CLZ prevents restenosis after CAS involving use of the CWS.

Acknowledgments

We acknowledge Drs Ryota Kimura and Hideaki Mishima at Ishinkai Yao General Hospital; Drs Akihira Kotani and Kazuhiro Yokoyama at Higashiosaka City Hospital; Drs Masashi Kotsugi and Kazuo Goda at Heisei Memorial Hospital; and Drs Hisashi Kawai, Ichiro Nakagawa, and Hiroyuki Nakase at Nara Medical University Hospital.

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