Investigation of Safe Termination of Antiplatelet Therapy after LVIS Stent-assisted Cerebral Aneurysm Coiling

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Objective: Patients who undergo stent-assisted cerebral aneurysm coiling require long-term antiplatelet therapy (AT). Recently, the low-profile visualized intraluminal support (LVIS) stent (LS) has been available for cerebral aneurysm treatment in Japan as a new design braided stent with excellent wall apposition due to manipulation even if the parent artery is tortuous, like the carotid siphon. The aim of this study was to evaluate whether AT could be terminated without increasing the risk of ischemic events among patients who have undergone LS-assisted cerebral aneurysm coiling.

Methods: In all, 15 consecutive patients with 15 unruptured aneurysms who underwent LS-assisted cerebral aneurysm coiling and were confirmed to have neointimal formation by follow-up angiography at 3 months were evaluated in this study. All aneurysms were located in the internal carotid artery (ICA). Dual AT was given for 1 month, and then a single antiplatelet agent was given for 2 months until confirmation of neointimal formation. After confirmation of neointimal formation, AT was terminated. The incidences of ipsilateral ischemic events and stent occlusion, as evaluated by angiography or contrast-enhanced MRA, after termination of AT were prospectively assessed.

Results: During follow-up, no ipsilateral ischemic events (mean, 10.3 months; range, 3.1–19.8 months) occurred, and no stent occlusion (mean, 8.0 months; range, 1–17.5 months) was observed in any cases.

Conclusion: Termination of the antiplatelet drugs 3 months after the procedure may be safe who underwent LS-assisted coil embolization.

Keywords ▶ antiplatelet therapy, cerebral aneurysm, coil embolization, low-profile visualized intraluminal support stent

Introduction

Patients who undergo the Enterprise stent (ES; Enterprise Vascular Reconstruction Device: Codman Neurovascular, Raynham, MA, USA)-assisted cerebral aneurysm coiling require long-term antiplatelet therapy (AT), but there are no definitive data to guide the duration of such therapy. Many groups of investigators have described using a 1- to 6-month period of dual AT with acetylsalicylic acid (ASA) (80–325 mg) and clopidogrel (75 mg), followed by lifelong ASA therapy in patients who have undergone coiling with ES.1-4) However, some studies have reported that cessation or modification of AT results in an increased risk of cerebral infarction due to delayed stent thrombosis. Incomplete endothelialization due to poor stent wall apposition may be an important cause of delayed stent thrombosis. However, it has been reported that AT termination at least 6 months postoperatively did not result in ischemic events among patients with neointima formation after ES-assisted cerebral aneurysm coiling.5) This suggests that, if neointima formation occurs after stent placement, AT can be terminated without ischemic events. Recently, the LVIS stent (LS; Low-profile Visualized Intraluminal Support device: MicroVention-Terumo, Tustin, CA, USA) has been...
available for cerebral aneurysm treatment in Japan as a new design braided stent that enables excellent wall apposition due to manipulation even if the parent artery is tortuous, like the carotid siphon (Fig. 1).

The aim of this study was to evaluate whether AT could be terminated without increasing the risk of ischemic events among patients who have undergone LS-assisted cerebral aneurysm coiling.

Materials and Methods

Between July 2016 and February 2018, 15 consecutive patients with 15 unruptured aneurysms (14 women; mean age, 68.1 years) underwent LS-assisted cerebral aneurysm coiling.

Treatment of unruptured aneurysms in our center is performed after careful assessment of perceived risk factors for rupture and consultation with our multidisciplinary cerebrovascular team and the patient.

Inclusion criteria for LS-assisted cerebral aneurysm coiling were as follows: 1) internal carotid artery (ICA) with wide-neck saccular aneurysm, defined as an aneurysm with a neck dimension $\geq 4$ mm or a dome-to-neck ratio <2; 2) parent vessel diameter $\geq 3$ mm; and 3) morphology or size of the aneurysm considered to indicate difficulty of treatment using balloon remodeling techniques.

The aneurysms were located in the ophthalmic artery ($n = 14$) or petrous ICA ($n = 1$). LSs were placed within the carotid siphon, except for one in the petrous ICA. The size and length of the LSs were as follows: 3.5 $\times$ 22 mm, $n = 10$; 4.5 $\times$ 18 mm, $n = 2$; 4.5 $\times$ 23 mm, $n = 3$. The mean aneurysm size was 6.58 mm (4.5–11.0 mm), and all aneurysms were saccular. One aneurysm was a recurrent aneurysm after clipping. Patients’ demographics and aneurysm information are provided in Table 1. All patients with cerebrovascular or cardiovascular disease requiring AT were excluded.

Follow-up angiography was performed at least 3 months after coiling in all patients, and neointima formation of LS was confirmed angiographically. Neointima formation within the LS was defined as present when the helical tantalum wire of the LS was angiographically embedded in multiple projections, except at the neck of the coiled aneurysm (Figs. 2D, 2E, and 3).

DSA studies were performed on a twin, flat-panel angiographic system (AXIOM Artis dBA or Artis Q BA Twin; Siemens AG, Erlangen, Germany) with a 1024 $\times$ 1024 matrix. Selective catheterization of the vessel harboring the aneurysm was performed. All treatment procedures and follow-up angiographies were performed by two interventional neuroradiologists with experience performing at least over 300 coiling cases. The angiographic and MRA findings were evaluated by two senior neuroradiologists, and clinical data were evaluated by a senior neurosurgeon. DSA was obtained in multiple views to confirm neointima formation within the LS. Dual AT (ASA 100 mg and clopidogrel 75 mg) was given for only 1 month, and then single AT (clopidogrel 75 mg) was given for 2 months until follow-up angiography, and after angiographic confirmation of the stent apposition, the antiplatelet agent was terminated.

Regimen of AT

Dual AT was given before coiling for at least 2 weeks. One week before coiling, P2Y12 reaction unit (PRU) values were checked by the VerifyNow Platelet Inhibition Assay (Accriva Diagnostics, San Diego, CA, USA) and confirmed to be within the effective range (60–239). In cases of PRU values over 240, prasugrel was administered, and the PRU value was confirmed to be within the effective range. One month after AT, if the PRU value was under 60, the dose of clopidogrel was decreased.

Assessments

The incidence of ipsilateral ischemic events (transit ischemic attack, retinal ischemia, and ischemic stroke) after termination of AT and the incidence of stent occlusion (as determined by contrast-enhanced [CE] MRA or DSA) at least 3 months after termination of AT was prospectively assessed.
All patients provided their informed consent. This study was approved by our institutional review board on April 26, 2016.

Results

After AT, clopidogrel was given to within the effective range in 14 of 15 cases. In one case, prasugrel was given instead of clopidogrel, and the effective range was confirmed. All 15 cases underwent LS-assisted cerebral aneurysm coiling without any periprocedural complications.

One month later, ASA was terminated without ischemic events, and clopidogrel was continued. At termination of ASA, the PRU value was checked, and the value was under 60 in three cases, and so the dose of clopidogrel was decreased.

In all cases, complete occlusion of the aneurysm and neointimal formation within the stent were confirmed by follow-up angiography.

AT was terminated in all patients at 3 months (Fig. 2). During follow-up (mean, 10.3 months; range, 3.1–19.8 months), no ipsilateral ischemic events or stent occlusion occurred in any of the cases. All patients underwent follow-up (mean, 8.0 months; range, 1–17.5 months) evaluation via CE-MRA or DSA. All aneurysms were completely occluded, and no in-stent stenosis was observed.

Discussion

After ES-assisted cerebral aneurysm coiling, several groups of investigators have used ASA (80–325 mg) and clopidogrel (75 mg) for a minimum of 1–6 months, followed by lifelong therapy with ASA alone, and some studies have reported that ischemic events can occur if AT therapy is modified or terminated.1–4) For example, Mocco et al.5) reported that delayed thrombotic events occurred in 7 of 213 (3%) patients after ES-assisted coiling in whom dual AT was terminated. In a similar context, Lee et al.6) reported that delayed infarction occurred in 11 of 261 (4.2%). Furthermore, Rossen et al.7) reported that discontinuation of clopidogrel therapy was associated with a 5% risk of ischemic events in patients after treatment with stent techniques. These reports suggest that some patients who have undergone ES-assisted procedures require lifelong dual AT. Some patients require temporary cessation of AT for surgery or biopsy, or permanent cessation of AT due to hemorrhagic complications. Indeed, the risk of major hemorrhage with dual AT is 2.1% per year as compared with 1.1% per year for aspirin alone among patients with recent lacunar strokes. Li et al. performed a prospective population-based cohort study of hemorrhagic complications and reported that, among 3166 patients on lifelong AT, 405 experienced first bleeding events (12.8%, n = 218 gastrointestinal, n = 45 intracranial, and n = 142 other) during a 13509 patient-year follow-up.8) Therefore, AT should be terminated if possible.

Incomplete stent apposition is associated with delayed ischemic events and the need for lifelong AT. Heller et al.9) reported that incomplete stent apposition of ES is associated with delayed ischemic events despite AT.9) Delayed ischemic events occurred in 8 (16%) of 50 cases, and all cases involved patients with incomplete stent apposition. In patients undergoing drug-eluting stent placement for
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Fig. 2 Case 1: Coil embolization with the LS for a left ophthalmic artery aneurysm. (A) Left carotid angiogram shows (right anterior oblique view) the ophthalmic artery aneurysm (arrow). (B) Unsubtracted image. Arrows indicate tantalum markers at either end of the LS. Arrowheads indicate two tantalum wires around the LS. (C) Left carotid angiogram immediately after coil embolization with the LS shows minor filling of the aneurysm (arrow). (D) Dyna CT after coiling with the LS shows excellent stent wall apposition at the carotid siphon. (arrows). (E) Follow-up angiogram 3 months after coil embolization with the LS. DSA image. Left carotid angiogram (right anterior oblique view) demonstrates complete occlusion of the aneurysm (arrow). (F) Unsubtracted image shows that the LS is embedded (arrowheads). Arrows indicate the tantalum markers at either end of the LS. (G) Follow-up angiogram at 5 months after AT termination. DSA image. Left carotid angiogram (right anterior oblique view) demonstrates complete occlusion of the aneurysm (arrowhead) and no in-stent stenosis (arrow). AT: antiplatelet therapy; LS: low-profile visualized intraluminal support device stent

coronary artery disease, several studies suggested that delayed arterial healing and stent malapposition may be important causes of very late stent thrombosis (thrombosis >1 year after stent deployment).\textsuperscript{10,11} Nomura et al.\textsuperscript{12} reported a case of very late in-stent thrombosis after ES-assisted coiling. This case was a 54-year-old woman with two unruptured aneurysms (ICA and anterior cerebral artery [ACA]). This patient underwent ES-assisted coiling for the ICA aneurysm first. Her postoperative course was uneventful. Although the stent apposition was incomplete, AT was terminated 12 months after the coiling. There was no event during at least 3 months after termination of AT. At 3 months after termination of AT, the patient underwent clipping for the distal ACA. However, cerebral infarction
due to in-stent thrombosis occurred 2 hours later, and the patient finally had a major stroke. They concluded it is possible that activation of platelet aggregation and blood coagulation due to operative stress and stent malaposition may cause very late in-stent thrombosis. Thus, prevention of operative stent malaposition is critical to enable termination of postoperative AT.

Delgado reported that a pre-procedure PRU value of < 60 or > 240 is the independent predictor of major perioperative thromboembolic and hemorrhagic complications after flow diverter system (Pipeline Embolization Device [PED]; Covidien/neurovascular, Irvine, CA, USA) procedures.\(^4\) Forty-four patients underwent 48 PED procedures at our institution during the study period. There were eight thromboembolic and hemorrhagic perioperative complications in our cohort (16.7%), four of which were major (8.3%). A pre-procedure PRU value of < 60 or > 240 (p = 0.02) and a technically difficult procedure (p = 0.04) were independent predictors of all perioperative complications. A pre-procedure PRU value of < 60 or > 240 (p = 0.004) and a history of hypertension (p = 0.03) were independent predictors of major perioperative complications.

Daou et al.\(^5\) reported that the mean patient age was 57 years. The mean last preprocedural PRU value was 132 (range: 1–382). The combined rate of major hemorrhagic complications (4%) and major thromboembolic complications (5.6%) was 9.6%. Analysis using Youden indices suggested an optimal PRU range of 70–150, with higher odds of complications outside this range (p = .01, odds ratio [OR] = 3 [1.2–7.5]). PRU < 60 was a significant predictor of hemorrhagic complications (p = .04, OR = 2.45 [1.01–5.9]), and PRU > 240 was a significant predictor of any thromboembolic complication (p = .04, OR = 3.6 [1.04–12]) and cerebral thromboembolic complications (p = .02, OR = 4 [1.2–14]). Target preoperative PRU values should be between 60 and 240 and ideally between 70 and 150. Values below and above this range carry higher odds of hemorrhagic and thromboembolic complications, respectively.

Long-term administration of dual AT is strongly associated with hemorrhagic complications; in particular, intracranial hemorrhage is associated with critical outcomes. Since coil embolization is performed to prevent cerebral aneurysm rupture, it is critical to ensure that hemorrhagic complications do not occur as a result of AT. We used the cutoff value proposed in the study to adjust the dose of AT to maintain the optimal PRU range preoperatively and postoperatively. This effort likely contributed to the prevention of ischemic and hemorrhagic complications during the perioperative and postoperative follow-up periods in the present study.

To prevent thrombus formation, AT should be continued until endothelialization of the stent takes place. Finn et al.\(^6\) performed an animal study using an electron microscope to examine endothelialization following bare-metal stent (BMS) placement. They observed complete neointimal coverage 14 and 21 days after BMS placement in the coronary arteries of pigs and the iliac arteries of rabbits, respectively.\(^7\) In humans, Ueda et al.\(^8\) observed complete neointimal coverage in all 13 patients that underwent follow-up angioscopic evaluations at 65–142 days (average 3 months) after BMS placement in the coronary artery. Lopes et al.\(^9\) reported postmortem histological evaluation of the implanted Neuroform stent for an ICA aneurysm. Complete endothelialization of the stent with moderate intimal hyperplasia and significant fibroelastic tissue formation along the aneurysmal neck were seen 4 months after stenting, but there was no significant stenosis. LS can have excellent wall apposition due to manipulation different to that for ES. Therefore, the early neointimal formation of LS is expected due to excellent wall apposition.

These studies suggest that neointimal formation of a stent occurs within 3 months after aneurysm coiling. Furthermore, given that stents were placed in non-atherosclerotic lesions in the present study, it was expected that neointimal formation would reduce the risk of in-stent thrombosis. Kanaan et al.\(^1\) examined the incidence of in-stent stenosis.
and occlusion due to neointimal formation in the stent following stent-associated coil embolization. They demonstrated that 3 (2.3%) of 133 patients (Neuroform 87.2%, ES 12%, Wingspan 0.8%) developed delayed stenosis or occlusion within an average of 5 months (2–7 months) after stenting. Specifically, one patient developed symptomatic in-stent obstruction, one patient developed asymptomatic 50% in-stent stenosis, and one patient developed asymptomatic in-stent obstruction at 2, 6, and 7 months after stenting, respectively.

There have been no reports of in-stent stenosis by LSs; although there was no in-stent stenosis at the 3-month follow-up in the present study, long-term follow-up is needed to further determine the risk of in-stent stenosis.

In the present study, neointimal formation was evaluated using DSA. With conventional stents, only the markers on both ends of a stent are visible by fluoroscopy. Thus, evaluation of stent malapposition is not possible where a stent is bent due to the inability to observe the stent itself. The use of a stent with helical tantalum wire would enable detection of stent malapposition, particularly where the stent is bent. In the present study, neointimal formation was defined as the presence of tantalum wire exterior to the lumen, which was visible by contrast enhancement of the wire. However, DSA alone is insufficient to fully evaluate neointimal formation since it was not possible to observe the perimeter of the lumen and the actual lumen itself. If intravascular ultrasound or optical coherence tomography is available for the intracranial arteries in the near future, it will be able to detect more accurate stent endothelialization. This information may be useful in achieving safe AT termination at an early stage. In principle, only those patients who do not have arteriosclerotic disease undergo stent-associated coil embolization; thus, AT administration should be terminated as soon as possible.

Although this study has the limitation of a nonrandomized, noncomparative study with a rather small sample size, a prospective comparative study involving a greater number of patients may be needed in the future to properly assess these initial results.

Conclusion

AT termination 3 months postoperatively did not result in ischemic events among patients who underwent LS-assisted cerebral aneurysm coiling. Neointimal formation of the LS may be a criterion for AT termination without increasing the risk of ischemic events.

Ethical Approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments and comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors declare that they have no conflict of interest.

References


