

Flow Diverter Therapy Using a Pipeline Embolization Device for 100 Unruptured Large and Giant Internal Carotid Artery Aneurysms in a Single Center in a Japanese Population

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Abstract

Flow diverters (FDs) have been developed for intracranial aneurysms difficult to treat with conventional endovascular therapy and surgical clipping. We reviewed 94 patients with 100 large or giant unruptured internal carotid artery (ICA) aneurysms treated with Pipeline embolization device (PED) embolization from December 2012 to June 2017 at Juntendo University Hospital. The patients' mean age was 63.4 years (range, 19–88), and there were 90 women 89.4%. Aneurysm locations were: C4 (45), C3 (4), and C2 (51) in ICA segments. Mean aneurysm size and neck width were 16.9 ± 6.8 mm and 8.3 ± 4.4 mm, respectively, in 40 symptomatic and 60 asymptomatic aneurysms. Follow-up catheter angiographies of 85 patients with 90 aneurysms showed no filling in 62 aneurysms (68.9%), entry remnant in 16 (17.8%), subtotal filling in 11 (12.2), and total filling in 1 (1.1%) with a mean follow-up of 10.2 ± 5.6 months. In-stent stenosis occurred in 1 patient and parent artery occlusion in 2 during follow-up. Hemorrhagic complications occurred in 4 (4.3%): delayed aneurysm rupture (2) and intraparenchymal hemorrhage (2). Ischemic complications with neurological symptoms occurred in 2 (2.1%): very delayed device occlusion (1) and intraprocedural distal embolism (1). Eighteen patients (45%) showed improvement in pre-existing cranial nerve dysfunction because of the aneurysm's mass effect, 3 patients (7.5%) worsened. One patient died of systemic organ failure unassociated with the procedure. Morbidity and mortality rates were 4.3% and 1.1%, respectively. PED embolization for unruptured large and giant ICA aneurysms is safe and efficacious. Physicians should be observant of characteristic risks associated with FD therapy.

Key words: intracranial aneurysm, flow diverter, Pipeline embolization device, Japanese population

Introduction

Endovascular therapy, particularly endosaccular coil embolization, has become a proven effective treatment option for intracranial aneurysms, as is surgical clipping.^{1–5)} However, for large and giant intracranial aneurysms endovascular therapy remains controversial because of the high recurrence and retreatment rates and the risk of postoperative rupture.^{6–8)} Recently, flow diverters (FDs) have been developed for the management of intracranial aneurysms that are challenging

for either endosaccular coil embolization or surgical clipping. FDs are stent-like devices with the mesh structure made by braiding metal wire. An FD can occlude the aneurysm sac thrombosis because of flow alternation when emplaced to cover the aneurysm neck. An FD can also preserve blood flow in small arteries and perforators covered with the device. The Pipeline embolization device (PED, Covidien, Irvine, CA, USA) is a popular FD and has currently become available for clinical therapy in Japan for large and giant unruptured or chronic ruptured aneurysms arising between the petrous and the superior hypophyseal artery segments of the internal carotid artery (ICA). We herein report our experience with FD therapy using the PED to treat unruptured large and giant ICA aneurysms in a Japanese population.

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Materials and Methods

We retrospectively reviewed the medical records, outpatient charts, and operative records of all 94 patients with 100 large or giant ICA aneurysms who underwent PED embolization from December 2012 to June 2017 at Juntendo University Hospital comprised this study's Japanese population. During this study period, there was a vertebrobasilar junction fusiform aneurysm case of off-label use. The case was excluded from this study and is currently being prepared as an original case report. The patients' mean age was 63.4 years (range, 19–88) at the initial treatment and 90 patients (89.4%) were women. All the patients gave written informed consent for the treatment before the procedures. The present series began with 6 patients with 6 aneurysms registered in the Japanese clinical trial of PED embolization in accordance with the institutional review board.

All the procedures were performed under general anesthesia and systemic heparinization. Aneurysm size, neck width, and parent artery diameters were measured using the appropriate images of 2D digital subtraction angiography with automatic calibration (Siemens Artis Q Biplane System, Siemens, Munich, Germany). In almost all cases, a 6-French ultra-long guiding sheath was positioned through transfemoral approach as distal as possible in the cervical ICA. A Navien distal support catheter (Covidien) was coaxially advanced as close as the aneurysm neck, and then a Marksman microcatheter (Covidien) for the PED delivery was navigated through the Navien 6-French ultra-long guiding sheath system beyond the neck to the distal ICA segment or horizontal segment of the middle cerebral artery with the assistance of a 0.014-inch microguidewire. Selection of the proper PED size was determined based on the caliber and length of the parent artery. The PED deployment techniques included a few maneuver combinations including Marksman microcatheter unsheathing and pushing and pulling with the catheter system, the PED delivery wire, and the Navien distal support catheter. Additional PEDs were deployed in a telescoping fashion in the event the aneurysm neck was not fully covered with a single device. A DynaCT (Axiom Artis dTA, Siemens Healthcare, Forchheim, Germany) was used to confirm the full opening of the device and adequate vessel wall apposition. In-stent balloon inflation using HyperForm (Covidien) or TransForm (Stryker, Fremont, CA, USA) balloon catheters was considered if necessary.

Follow-up angiography

Catheter angiographies were generally scheduled at 6 months and 1 year after the procedure. When the 1-year follow-up angiography confirmed complete aneurysm occlusion without significant in-stent stenosis, annual follow-ups with magnetic resonance angiography were scheduled thereafter. If not, annual follow-up angiographies were done until complete aneurysm occlusion with resolution and/or no further deterioration of in-stent stenosis was confirmed.

Antithrombotic therapy

All the patients received dual antiplatelet therapy (DAPT) with a daily dose of 100 mg aspirin and 50–75 mg clopidogrel at least 10 days before the procedure. Platelet inhibition levels were tested routinely using the VerifyNow P12Y12 Assay (Accumetrics, San Diego, CA, USA) the day before the procedure with a target reaction unit of <550 for aspirin and <230 for clopidogrel. DAPT was basically continued until 1 year after the procedure. If the platelet inhibition did not achieve the satisfactory levels, the patient received additional clopidogrel of 50–75 mg (a total of 100–150 mg) and cilostazol 100–200 mg immediately before the procedure and continued for 1 year. If the 1-year follow-up angiography showed complete aneurysm occlusion without significant in-stent stenosis, DAPT was discontinued, and single antiplatelet therapy (SAPT), either aspirin or clopidogrel, was maintained for as long as 2 years after the procedure. Patients with incomplete aneurysm occlusion and/or significant in-stent stenosis should continue with SAPT until angiographic confirmation is made of complete aneurysm occlusion and/or there is no further deterioration of in-stent stenosis.

Results

Six of 94 patients had bilateral ICA aneurysms treated with PED embolization. The aneurysms were located in the C4 (45), C3 (4), and C2 (51) ICA segments. The mean aneurysm size and neck length were 16.9 ± 6.8 mm and 8.3 ± 4.4 mm, respectively. There were 40 symptomatic and 60 asymptomatic aneurysms. All the patients harboring symptomatic aneurysms presented with cranial nerve dysfunction associated with the aneurysm's mass effect. Fifty asymptomatic aneurysms were detected incidentally and the remaining 10 were recurrent aneurysms after endosaccular coil embolization (7) or clipping (1), associated with aneurysm rupture (1), and symptomatic unruptured aneurysm (1). A total of 142 PEDs were used (mean per aneurysm, 1.4). Seventy-seven aneurysms

were treated with a single device and the remaining 23 with multiple devices in telescoping or overlapping fashions: 2 devices (15), 3 (3), or more (5), at most 8 devices were used per aneurysm. Although there were no established criteria for adjunctive endosaccular coil embolization, it was considered when the aneurysm was located in the subarachnoid space with the jet flow into the sac associated with a narrow neck, irregular shape, and an aneurysm size of ≥ 15 mm. As a result, 34 aneurysms (34%) were treated with PED placement and adjunctive endosaccular coil embolization.

Angiographic outcomes

The degree of occlusion, according to the OKM (O'Kelly-Marotta) grading scale (no filling, entry remnant, subtotal filling, total filling), and significant in-stent stenosis of $\geq 50\%$, according to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method, were evaluated by all the authors in this study.^{9,10} Eighty-six patients with 91 aneurysms underwent follow-up catheter angiography with a mean follow-up period of 10.2 ± 5.6 months (Table 1). The latest angiographic outcomes showed no filling in 63 patients (69.2%), entry remnant in 16 (17.6%), subtotal filling in 11 (12.1%), and total filling in 1 (1.1%). Among the completely occluded aneurysms, there were no recurrences on angiographic follow-up studies. Significant in-stent stenosis without neurological symptoms occurred in one patient (1.2%) who underwent percutaneous balloon angioplasty to resolve the stenosis. However, a direct carotid cavernous fistula (DCCF) developed because of the vessel dissection during balloon inflation. The patient underwent internal coil trapping of the dissected parent artery without clinical modification. Spontaneous parent artery occlusion (PAO) occurred in three patients during the follow-up period (3.5%): asymptomatic (2) and symptomatic (1). Eight patients did not undergo a scheduled follow-up catheter

angiography due to: the short follow-up duration (5), a delayed aneurysm rupture (2), and an unsuitable systemic condition for catheter angiography (1).

Complications

Symptomatic ischemic complications occurred in two patients (2.1%). One patient suffered from very delayed (>2 years after the procedure) device occlusion with a major ischemic stroke associated with discontinuation of antiplatelet therapy. This case was reported in the literature.¹¹ Another patient suffered a minor stroke immediately following the procedure. Diffusion weighted-imaging on the day of the procedure showed multiple high-intensity signals (HISs) in the treated cerebral hemisphere because of distal embolisms and/or parent artery flow insufficient during the PED deployment. Fortunately, the patient's symptoms were transient, and the patient fully recovered within 30 days after the procedure. Ninety-three patients underwent a diffusion-weighted imaging study within 3 days after the procedure. Among those, 83 patients (89.3%) showed new HISs suggesting microembolic lesions.

Hemorrhagic events occurred in four patients (4.3%): DCCF due to rupture of a treated aneurysm (2) and remote intraparenchymal hemorrhage (2). Two patients suffering from delayed aneurysm rupture developed a DCCF, one on day 4 and the other 2 weeks after the procedure. Those patients underwent transvenous coil embolization successfully with preservation of the ICA. The first patient among those was reported in the literature.¹² Two patients suffered from remote intraparenchymal hemorrhage, one patient developed a large ipsilateral frontal lobe hematoma on the day after the procedure. One of the causes was thought to be excessive platelet inhibition because of the patient's four reaction units for clopidogrel and 584 for aspirin (The VerifyNow System, Accumetrics) at the onset. Although the patient suffered from hemiplegia and dysphasia, there was steady but gradual improvement during a 3-month stay in the hospital. The patient was transferred to the rehabilitation center being able to walk without a cane. The other patient developed a small, asymptomatic intraparenchymal hematoma in the temporal lobe of the PED deployed side 4 days after the procedure. Although the patient's platelet inhibition was at an acceptable level with the 397 reaction units for clopidogrel and 155 for aspirin just before the procedure, the load of clopidogrel decreased from 50 to 25 mg. The 6-month follow-up angiography showed the PAO without any neurological deficits.

Table 1 Angiographic outcome of aneurysms treated with pipeline embolization device embolization

Follow-up period	6 months	1 year	Latest
Number of aneurysms	91	52	91
No filling	59 (64.8%)	36 (69.2%)	63 (69.2%)
Entry remnant	18 (19.8%)	10 (19.2%)	16 (17.6%)
Subtotal filling	11 (12.1%)	5 (9.6%)	11 (12.1%)
Total filling	3 (3.3%)	1 (1.9%)	1 (1.1%)

Clinical outcomes

Morbidity and mortality were defined as a deterioration of the mRS score to > 0 at 30 days after the procedure. Four patients had a deteriorated mRS score and one patient, an 84-year-old woman with a symptomatic giant carotid cavernous aneurysm, died 32 days after the procedure because of a complication unrelated to the procedure or the device, mainly pneumonia leading to systemic organ failure. Therefore, the morbidity and mortality rates were 4.3% and 1.1%, per patient and 4% and 1%, per aneurysm, respectively. Regarding the outcomes of cranial nerve dysfunction due to the aneurysm's mass effect: 18 of 40 (45%) symptomatic aneurysms showed some improvement or complete resolution, 19 (47.5%) were unchanged, and 3 (7.5%) were deteriorations during the follow-up period (mean, 13.5 months, range, 1–45 months). In detail: the optic nerve showed improvement (3), unchanged (5), worsening (2); the oculomotor nerve improvement (7), unchanged (9); the abducens nerve improvement (8), unchanged (3), worsening (1); and the trigeminal nerve unchanged (2). Motor nerve dysfunction tended to improve after PED embolization; however, the sensory nerve dysfunction did not improve. No patients exhibited *de novo* cranial nerve dysfunction after the PED embolization of asymptomatic aneurysms.

Discussion

The significant drawbacks of endosaccular coil embolization for large and giant intracranial aneurysms are a paucity of both the anatomical durability and efficacy of preventing rebleeding in the mid- to long-term period.^{7,8,13,14} Because the development of intracranial aneurysms is because of parent artery wall damage that is a pathologically degenerative change in the internal elastic lamina,^{15–17} complete cure of intracranial aneurysms requires vessel wall reconstruction. Although PAO is an effective option for large and giant ICA aneurysms; particularly, those presenting with mass effect in the surrounding neural structure, there is a risk of developing *de novo* aneurysms because of flow change. Furthermore, if the patient's artery did not have sufficient collateral blood flow, bypass surgery (i.e., STA-MCA [superficial temporal artery-to-middle cerebral artery] anastomosis or a high flow) would be required.^{18–20} On the other hand, FDs are ideal treatment devices because they promote endoluminal and neointimal growth leading to parent vessel reconstruction while preserving antegrade blood flow.

Regarding the angiographic outcome, the pipeline for uncoilable or failed aneurysms (PUFS) data showed a high rate of complete occlusion after PED

therapy of 73.6% and 86.8% at 6 months and 1 year, respectively.²¹ In the present series, the rates of complete occlusion on angiographic evaluation at 6 months and 1 year were 64.4% and 72.6%, respectively. Although definitive reasons for the poorer occlusion rates in the present series compared to the PUFS data are not clear, it may likely be due to the relatively new technique associated with limited experience and the pharmaceutical law limiting the number of devices to only one per aneurysm. There were no aneurysm recurrences after the confirmation of complete occlusion in the PUFS 5-year results.²² The present series also showed no aneurysm recurrences after the confirmation of complete occlusion on angiographic evaluation.

Pipeline embolization device therapy complications include: hemorrhagic event, thromboembolic event, branch, and/or perforating artery occlusion, PAO, in-stent stenosis, and worsening of the aneurysm's mass effect. Kallmes et al. reported in their pooled analysis of three large pipeline embolization studies that there were rates of 3.7% ischemic stroke, 2.0% hemorrhagic stroke, and 7.1% significant neurological sequelae or neurological death.²³ In the present series, symptomatic ischemic stroke and hemorrhagic stroke occurred at 2.1% and 4.3%, respectively.

Possible causes of ischemic events consist of insufficient platelet inhibition, insufficient device opening, poor vessel wall apposition, compromise of covered surrounding branches or perforating arteries, and in-stent stenosis. Brinjikji et al.²⁴ reported perforating artery infarction in 3%, and posterior circulation aneurysms have a higher risk compared to that of anterior circulation aneurysms. There were no symptomatic branch or perforating artery occlusions in the present series because all the aneurysms were located in the proximal ICA. The incidence of HISs after FD therapy is frequent. Iosif et al.²⁵ and Heller et al.²⁶ reported the incidence of HIS after FD therapy as 92.1% and 52%, respectively. The present series also showed an 83.8% incidence of HIS after PED therapy. Park et al.²⁷ reported a 37.3% incidence of microembolic lesions after endovascular coiling of unruptured intracranial aneurysms. Although most microembolic lesions after FD therapy are asymptomatic, the frequency is higher than that with conventional endosaccular coil embolization. Distal emboli during complex device deployment procedures may be the main cause of this higher frequency. Becske et al.^{21,28} reported 1.1% (1/91) and 4.5% (3/66) of carotid occlusion in the PUFS 1- and 3-year follow-ups, respectively. The PUFS 6-year follow-up study showed 6.06% risk of PAO or in-stent stenosis of $\geq 50\%$; however, none of them showed any neurological symptoms.²²

In the present series, PAO and significant in-stent stenosis occurred in 3.5% and 1.2% of the aneurysms, respectively. PAO particularly occurred when there was a discontinuation or reduction of antiplatelet therapy. Although, to our knowledge, while there is no appropriate, universal regimen of antiplatelet therapy, long-term antiplatelet therapy may be mandatory to prevent PAO. A previous study on stent-assisted coil embolization showed 0.6% and 3.5% risk of PAO and in-stent stenosis, respectively.²⁹⁾ Although the rates of PED embolization for PAO and/or in-stent stenosis is slightly more frequent compared to that of conventional stent-assisted coil embolization, the risk of clinical modification is extremely low.

Hemorrhagic events of PED embolization mainly consisted of aneurysm rupture and intraparenchymal hemorrhage. Rouchaud et al.³⁰⁾ reviewed 443 articles reporting on flow diverter therapy. Among those articles, 53 reported on delayed intracranial hemorrhage. There were 81 aneurysm ruptures and 101 intraparenchymal hemorrhages. Although the risk of aneurysm rupture after FD therapy is very low (0–1.1%), the outcome is extremely poor when it occurs. The anatomical risk factors of delayed aneurysm rupture were large and giant aneurysms associated with mass effect, saccular shape with a high aspect ratio > 1.6, and morphologic characteristics predisposed to an inertia-driven inflow.³¹⁾ The reasons of delayed aneurysm rupture might be increased intra-aneurysmal pressure because of flow alternation (i.e., blood outflow restriction more than the inflow), weakened aneurysm wall as a result of the protease formation associated with aneurysm sac thrombosis and accompanying inflammation.³¹⁾ The combination of FD therapy and simultaneous endosaccular coil embolization is being considered for preventing delayed aneurysm rupture.^{32,33)} In the present series, two aneurysms which developed delayed aneurysm ruptures were not treated with combination FD therapy and endosaccular coil embolization. The risk of intraparenchymal hemorrhage is reported as 2–3% among which 82.2% occurred in the treated vascular territory and 17.8% in the nontreated vascular territory.³⁰⁾ In the present series, intraparenchymal hemorrhage occurred in two patients (2.1%). The estimated causes of intraparenchymal hemorrhage are: antiplatelet therapy, hyperperfusion after parent artery reconstruction, hemorrhagic transformation of ischemic lesions, and wire perforation during device deployment. When intraparenchymal hemorrhage occurred, the outcome was also extremely poor.³⁰⁾ The PUFs study showed a major ipsilateral stroke or neurologic death rate of 5.6% or 2.6%, respectively.²¹⁾ Kallmes et al.³⁴⁾

reported in the multicenter study that the overall neurologic morbidity and mortality rate was 9.2% in the patients with unruptured ICA large aneurysms.³⁴⁾ In the pooled analysis of 3 large studies of PED embolization, the major neurological morbidity and mortality rates were 5.7% and 3.3%, respectively.²³⁾ The morbidity and mortality rates (4.3% and 4.1%) in the present series were comparable with those in the literature.

Because completely occluded aneurysms after PED embolization shrink, the resolution of cranial nerve palsy due to the aneurysm's mass effect can be expected. Sahlein et al.³⁵⁾ reported that the neuro-ophthalmological outcomes after PED embolization showed some improvement (64%), unchanged (33.4%), and worsened (2.6%) during the 6-month follow-up. In our series, the outcomes of cranial nerve dysfunction because of the aneurysm's mass effect were some improvement or complete resolution (45%), unchanged (47.5%), and deterioration (7.5%) during the mean follow-up period of 13.5 months. Van Rooij and Sluzewski³⁶⁾ reported the change of cranial nerve palsy in 17 selectively coiled symptomatic aneurysms: unruptured large and giant carotid aneurysms had resolved (3), improved (10), and remained unchanged (4). To our knowledge, there are no prospective comparative data, in the literature, on the outcome of cranial nerve dysfunction directly comparing FD therapy and endosaccular coil embolization.

Limitations

Because this study had the limitations of it being a retrospective study, with a brief follow-up period, and of a single center experience, these factors must be considered when interpreting the results.

Conclusion

Pipeline embolization device embolization is an effective treatment for unruptured large and giant ICA aneurysms. However, physicians should be observant of characteristic risks associated with the FD device and the procedure.

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Conflicts of Interest Disclosure

Hidenori Oishi receives 1 million yen or more annually from Medtronic Japan for attending conferences

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