

Long-term Follow-up Results after Flow Diverter Therapy Using the Pipeline Embolization Device for Large or Giant Unruptured Internal Carotid Artery Aneurysms: Single-center Retrospective Analysis in the Japanese Population

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Abstract

Flow diverter (FD) therapy using Pipeline embolization device (PED) has become an important alternative to treat internal carotid artery (ICA) aneurysms. Herein, we report the long-term outcome for 3 years after FD therapy using PED for ICA aneurysms in Japan. The patients who underwent angiographical and/or clinical follow-up for 3 years after the FD therapy using PED of large or giant unruptured ICA aneurysms from December 2012 at our university hospital are the subjects of this study. We retrospectively reviewed the in- and outpatients' medical charts, and written operative and radiological records. There were 84 patients with 90 aneurysms who could be clinically and/or angiographically followed up for 3 years. Of these, 7 aneurysms were only available for clinical follow-up. Of the remaining 83 aneurysms, 6 aneurysms had vessel occlusion due to stent thrombosis or parent artery occlusion, and 60 of the remaining 77 (77.9%) had complete occlusion. In multivariate analysis, older age (>70 years), wide neck, and non-adjunctive coiling contributed statistically significantly to incomplete occlusion. Of the 84 patients, 2 patients (2.4%) had delayed complications between 6 months and 3 years after the initial FD placement. Three patients (3.6%) had poor outcome due to postoperative major stroke complications, 2 of which were acute complications. The long-term results after FD therapy are good both angiographically and clinically. Endothelialization of the aneurysmal neck and intra-aneurysmal thrombosis contribute to complete occlusion. The primary reason for the somewhat low complete occlusion in Japan may be the patients are generally older.

Keywords: aneurysm, flow diverter, long-term outcome

Introduction

Endovascular coil embolization has been proved to be an effective treatment modality for intracranial aneurysms but has anatomical and/or clinical limitations for application to large or giant aneurysms,

which are associated with incomplete aneurysm occlusion leading to high rates of recurrence and retreatment.^{1–4)} Open surgical treatment of large or giant aneurysms can be accomplished with direct clip reconstruction, aneurysm trapping with or without surgical bypass, and parent artery occlusion (PAO) with or without surgical bypass, but these procedures are also associated with high morbidity and mortality rates.^{5–8)} Recently, the flow diverter (FD) was developed as an innovative endovascular device intended to disrupt the blood flow into the aneurysm sac with preservation of the antegrade

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flow in the parent artery, surrounding small arteries, and perforators.⁹⁾ FD placement using the Pipeline embolization device (PED) (Covidien/Medtronic, Irvine, CA, USA) has become an important alternative to treat large or giant internal carotid artery (ICA) aneurysms.^{10,11)} The PED is currently the most common FD device in the world and was first approved for use in Japan in October 2015. We report long-term follow-up results for 3 years after FD therapy using the PED for large or giant ICA aneurysms in a Japanese population.

Materials and Methods

This study included patients who underwent angiographical and/or clinical follow-up for 3 years after FD therapy using the PED for large or giant unruptured ICA aneurysms at our university hospital. In- and outpatients' medical charts, and written operative and radiological records were retrospectively reviewed. FD therapy was started at our university hospital from December 2012 as a clinical trial and approved from October 2015 in Japan. The treatment indication for FD therapy was unruptured aneurysm of the petrous through superior hypophyseal segments of the ICA, which were larger than 10 mm in diameter with a neck of at least 4 mm. This retrospective study was approved by the ethics committee of our university hospital (No. 19121) and conducted in accordance with the Declaration of Helsinki (2013).

Radiological and clinical follow-up procedures

Catheter angiography was performed at 6 months and/or 1 year after the procedure. All endovascular procedures and follow-up catheter angiography were performed using the Artis Q BA Twin Biplane System (Siemens, Munich, Germany) with 3-dimensional (3D) digital subtraction angiography (DSA) images. Fusiform type was defined as "circumferential dilations of an intracranial artery without an ostium or neck."¹²⁾ The neck diameter of the fusiform type was measured from the beginning of the dilatation to the end of the vessel. The degree of aneurysm occlusion, according to the O'Kelly-Marotta (OKM) grading scale (A, total filling; B, subtotal filling; C, entry remnant; D, no filling), and significant in-stent stenosis of 50% or more, according to the Warfarin–Aspirin Symptomatic Intracranial Disease method, were assessed by all authors independently. If angiography at 6 months and/or 1 year showed OKM grade D without significant parent artery stenosis, silent 3D time-of-flight magnetic resonance (MR) angiography was performed annually. Silent MR angiography (GE Healthcare, Milwaukee, WI,

USA) is a useful radiological modality for less invasive anatomical evaluation after FD therapy using PED for intracranial aneurysms.¹³⁾ If 1-year follow-up angiography could not confirm OKM grade D and/or showed significant parent artery stenosis, annual follow-up angiography was recommended. Clinical outcomes were evaluated at discharge, 6 months, 1 year, and annually at outpatient visits.

Antiplatelet therapy

All patients received dual antiplatelet therapy with a daily dose of 100 mg aspirin and 50–75 mg clopidogrel, according to body weight, at least 10 days before the procedure. Platelet inhibition levels were analyzed using the VerifyNow P2Y12 Assay (Accumetrics, San Diego, CA, USA) on the same day or just before the procedure. The reaction units of aspirin and clopidogrel were targeted for <550 and <230, respectively. If the reaction units did not reach the target values, the doses of the hyporesponsive antiplatelet agent were increased by up to 2 times. Postoperative antiplatelet therapy was continued at 100 mg aspirin and same dose of clopidogrel until 6 months after operation. After 6 months, clopidogrel was gradually reduced to aspirin alone based on the results of angiography.

Endovascular procedure

All patients underwent endovascular procedures under general anesthesia and systemic heparinization. Angioarchitecture including the aneurysm diameter, neck width, and parent artery diameter was evaluated using the appropriate images of 2-dimensional DSA with automatic calibration referring to 3D DSA images. The procedure was performed using the same system of conventional methods as previously reported.¹⁴⁾ If the aneurysm neck was not fully covered with a single device, additional PEDs were deployed using a telescoping technique. No criteria were established for adjunctive endovascular coil embolization, but this was considered if the aneurysm was located in the subarachnoid space with jet flow into the sac associated with a narrow neck, irregular shape, or aneurysm size of more than 15 mm. Overlap stent was used in cases where eclipse sign did not occur and flow diversion effect was weak or in cases where the contrast medium continued to flow into aneurysm.

Results

Subjects

A total of 112 patients with 119 large or giant ICA aneurysms underwent FD therapy using the

PED at least 3 years before beginning the data collection. No patient had acutely ruptured or previously coiled aneurysms with intracranial stent. Twenty-eight patients with 29 aneurysms were lost to follow-up before 3 years after FD therapy. Twenty-four patients with 25 aneurysms were lost to follow-up because of various reasons (e.g., moving and inconvenience). Four patients died, 2 of unknown etiology, 1 of cancer, and 1 of pneumonia.

Clinical outcome

Table 1 shows the clinical characteristics of 84 patients with 90 aneurysms who were clinically followed up for 3 years. Postoperative complications occurred in 4 cases, including the acute phase. Of these, 2 were acute complications and

Table 1 Clinical characteristics of 84 patients with 90 aneurysms

Parameters	Data
Age, mean \pm SD, years	61.5 \pm 13.2
Sex, female/male (% of females)	73/11 (86.9%)
Aneurysm side, right/left	42/48
Aneurysm locations, n (%)	
C2	44 (48.9)
C3	4 (4.4)
C4	42 (46.7)
Aneurysm measurement, mean \pm SD, mm	
Dome size	16.6 \pm 6.8
Neck size	8.4 \pm 4.8
Aneurysm morphology, n (%)	
Saccular	35 (38.9)
Fusiform	55 (61.1)
Asymptomatic aneurysms, n (%)	51 (56.7)
Headache unrelated to aneurysm, n (%)	9 (10.0)
Symptomatic aneurysms, n (%)	30 (33.3)
Visual pathway dysfunction	7 (7.8)
Extraocular nerve dysfunction	22 (24.4)
Pituitary dysfunction	1 (1.1)
Number of implanted PED devices, mean \pm SD	1.4 \pm 1.1
Number of implanted PED devices, n (%)	
1	70 (77.8)
2	12 (13.3)
\geq 3	8 (8.9)
Adjunctive coiling, n (%)	29 (32.2)

PED: Pipeline embolization device, SD: standard deviation.

2 occurred between 6 months and 3 years postoperatively. Two patients with 2 aneurysms suffered from symptomatic ischemic complications leading to worsening of the clinical outcome: acute phase (day 0) due to incomplete device opening in 1 and very delayed phase in 1 (26 months after FD therapy; 4 months after single antiplatelet therapy withdrawal). Previously, we reported this very delayed ischemic complication case.¹⁵⁾ There were 2 hemorrhagic complications. One patient developed posttreatment intraparenchymal hemorrhage on the first postoperative day, and one patient developed iatrogenic carotid cavernous fistula 6 months after the operation, but PAO was performed, and the patient had no obvious neurological deficit. In summary, of the 84 patients, 3 patients (3.6%) had poor outcome due to postoperative major stroke complications, 2 of which were acute complications.

Resolution of aneurysm symptoms

Of the 22 cases of extraocular nerve dysfunction, symptom improvement was obtained in 17 cases (77.3%), no change in 5 cases (22.7%), and no worsening of symptoms in any case. On the other hand, of the 7 patients with visual pathway dysfunction, 3 cases (42.8%) showed improvement, 2 cases (28.6%) showed no change, and 2 cases (28.6%) showed worsening. One patient suffered from panhypopituitarism due to compression of a huge ICA cavernous aneurysm but did not require hormone replacement therapy 1 year after the FD therapy.

Radiological outcome

Trends in the occlusion rate of aneurysms after PED placement are shown in Fig. 1. Seventy-one patients with 77 aneurysms were angiographically followed up for 3 years. The angiographical outcomes for these 71 patients, excluding 7 patients with PAO, were as follows. After 6 months, the occlusion rates were 1 (1.3%) for OKM A, 10 (13.0%) for OKM B, 16 (20.8%) for OKM C, and 50 (64.9%) for OKM D. After 1 year, the occlusion rates were 1 (1.3%) for OKM A, 6 (7.8%) for OKM B, 11 (14.3%) for OKM C, and 59 (76.6%) for OKM D. After 3 years, the occlusion rates were 1 (1.3%) for OKM A, 6 (7.8%) for OKM B, 10 (13.0%) for OKM C, and 60 (77.9%) for OKM D.

Univariate and multivariate analyses are shown for age, sex, location, form, aneurysm dome and neck size, and presence of adjunctive coil (Table 2). Univariate analysis showed that aneurysm shape, dome and neck size, and concomitant coils were influential factors in aneurysm occlusion status.

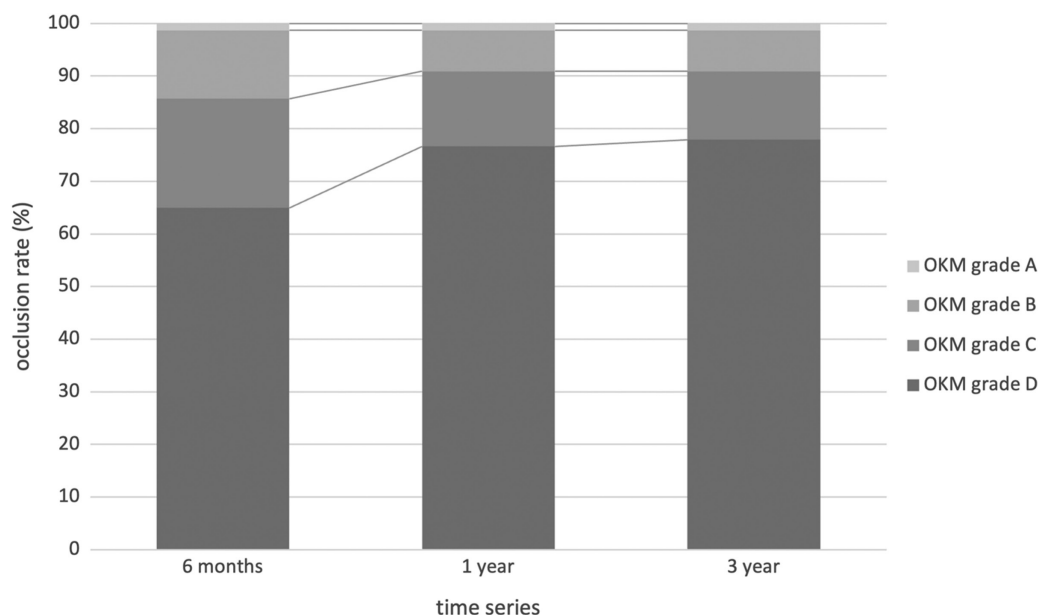


Fig. 1 Trends in occlusion rates after PED for intracranial aneurysms. OKM grade indicates O’Kelly-Marotta grade. PED: Pipeline embolization device.

Table 2 Univariate analysis and multivariate analysis of complete occlusion and incomplete occlusion for intracranial aneurysms

	Univariate analysis		Multivariate analysis	
	Odds ratio	P Value	Odds ratio	P Value
Age, >70 years	2.71	0.128	71.7	0.00601
Sex, male	0.361	0.155	6.02	0.169
Location				
C2	Control	NA	Control	NA
C3	0.265	0.213	5.96×10^{-8}	0.995
C4	1.06	0.333	0.158	0.234
Morphology, saccular (control: fusiform)	0.127	0.000764	0.0625	0.066
Aneurysm size				
Dome size (control: 10–14.9 mm)				
15–24.9 mm	3.64	0.0421	2.76	0.287
≥25 mm	32.8	0.00405	21	0.13
Neck size (control: <5.9 mm)				
6–9.9 mm	2.94	0.202	10.3	0.0948
≥10 mm	34.7	0.000383	39.7	0.0339
Adjunctive coiling	0.0714	0.013	0.0325	0.0349

NA: not applicable.

Multivariate analysis found that age over 70 years, aneurysm neck size, and concomitant coils were significant in influencing aneurysm occlusion status.

Of the 77 aneurysms, only 1 case underwent additional FD implantation, and even after additional implantation, complete occlusion was not achieved.

Parent artery stenosis

One of the 71 patients with radiological evaluation for 3 years suffered from significant parent artery stenosis at 1 year follow-up. The patient underwent percutaneous transluminal angioplasty.

Cases with long-term changes

After long-term follow-up, radiologically changes were observed in 6 cases. The long-term radiologically change is defined as the image change from the first to the third year follow-up. Of these, 2 cases had progressive complete occlusion, 2 cases had in-stent occlusion due to antiplatelet reduction and complicated FD placement, and 2 patients had recurrence.

Discussion

Low rate of complete occlusion after FD

This is the first study of the long-term outcome after FD device placement for large or giant intracranial aneurysms in the Japanese population. The results of this study confirmed the safety of FD treatment, with no rupture of cerebral aneurysms observed during the 3-year long-term follow-up period after FD implantation. On the other hand, the complete occlusion rate was 77.9% after 3 years of long-term follow-up, which was lower than that of 81.9–93.3% in the past large-scale studies.^{10,16,17} The PUFs study found a more pronounced difference in complete occlusion rate of 93.4% at the same follow-up duration of 3 years.¹⁸ There are 3 possible reasons for the low complete occlusion rate with FD therapy in Japan.

Patient background is elderly

First, the patient characteristics of our study subjects. The average age of patients in previous large studies was 54.6–57.0 years,^{10,16,17} which is younger than the average age of our patients of 61.5 years. Older patients tend to have lower occlusion rates.^{19–21} Our multivariate study found that the older age group of >70 years had a significantly worse occlusion rate compared to the younger age group of 60–69 years.

Complete occlusion of the aneurysm after FD placement requires intra-aneurysmal thrombosis and aneurysmal neck endothelialization. Our multivariate analysis also validated the effect of adjunctive coil embolization on the occlusion rate for intra-aneurysmal thrombosis. The mechanism of aneurysmal neck endothelialization after FD implantation is still unclear but is believed to involve a repair mechanism for intimal damage.²² The occlusion rate after FD placement is lower in elderly patients

due to a weakened intimal repair mechanism.²⁰ Furthermore, our multivariate analysis showed that aneurysm dome size was not a significant factor but neck size had a specific effect on aneurysm occlusion, suggesting that endothelialization of the aneurysm neck is an important factor in occlusion after FD placement, and so is an important factor in post-FD therapy. On the other hand, fusiform type aneurysms were statistically significant in univariate analysis, but not in multivariate analysis, suggesting the importance of the area covered by the FD rather than its shape in the occlusion of cerebral aneurysms.

The high average age in this study reflects the higher life expectancy in Japan compared to other countries, so that the elderly are treated more aggressively, and also the availability of head MR imaging scanners is higher, so examination is more common. In fact, our patient background showed that the aneurysm was more easily detected in elderly asymptomatic patients. The percentage of patients without neurological symptoms was 66.7%, which is higher than in previous studies.^{10,16,17}

Device insurance issues

Second, the cost and insurance coverage of the FD device is important. In Japan, the PED was approved by the pharmaceutical affairs bureau in 2015, but the number of devices that could be used was limited to one per procedure at the beginning. The mean number of devices used in the PUFs was 3.1, whereas the average number of devices used in the PREMIER was 1.1.^{10,17} Therefore, the differences in aneurysm occlusion rates between PUFs and PREMIER may be due to the difference in the number of FD devices used. In addition, the use of coils is limited from the perspective of insurance assessment, which may have some influence on the reduced occlusion rate.

Impact on CYP2C19

Third, we found low rates of formation of neointimal hyperplasia, which is thickening of the vessel wall after FD implantation and is a rare cause of delayed cerebral ischemia. Complete occlusion rate can be achieved in patients with high levels of neointimal hyperplasia.²³ The rate of vascular stenosis after FD implantation is 1.8–3.3%,^{10,16,17} and especially in the third year of the PUFs, the rate of vascular stenosis was 13.1% and worsened over time.¹⁸ In comparison, the present study showed a lower rate of parent artery stenosis after FD placement (1.3%), possibly due to the fact that patients are older and less likely to have neointimal hyperplasia. Furthermore, neointimal hyperplasia is

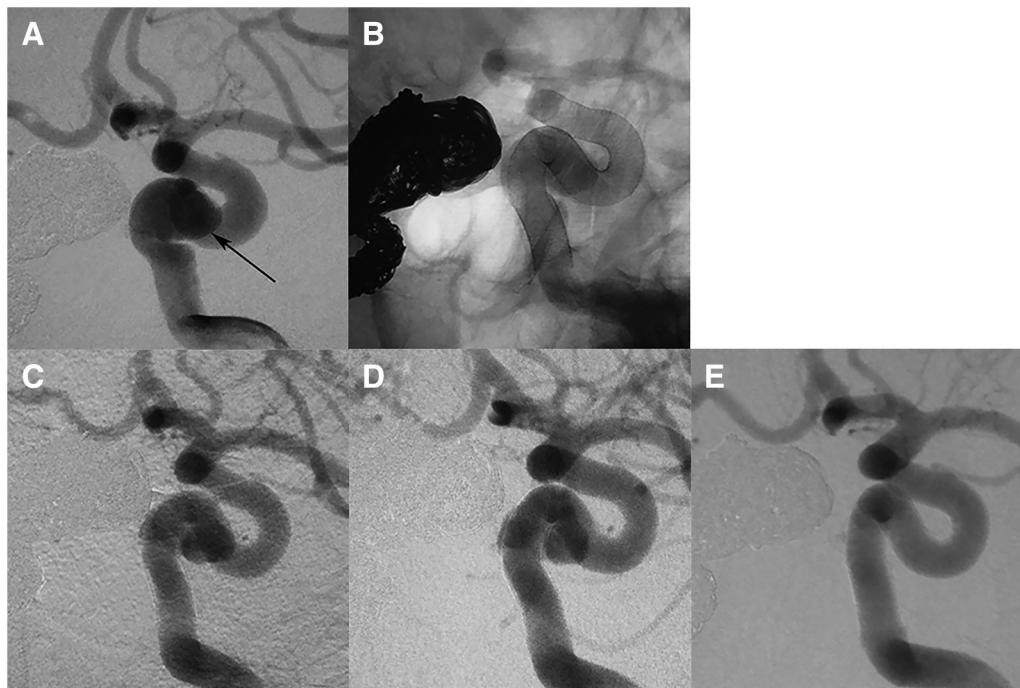


Fig. 2 (A) Left internal carotid angiogram showing a large, regular, fusiform aneurysm with dome size of 13.1 mm and neck size of 8.3 mm located in the C4 segment of the ICA (black arrow). PAO was performed for the right internal carotid aneurysm 2 years earlier, and the left internal carotid angiogram showing collateral blood flow through the anterior communicating artery. (B) Multiple PED was placed (black arrow). (C and D): Angiogram at 6 months and 1 year later showing incomplete occlusion of OKM grade B. (E) Angiogram at 3 years later showing complete occlusion of OKM grade D. ICA: internal carotid artery, OKM: O'Kelly-Marotta, PAO: parent artery occlusion, PED: Pipeline embolization device.

inhibited by antiplatelet agents, especially P2Y12 inhibitors.²⁴⁾ Polymorphism of CYP2C19 is present in 20% of Asians, including Japanese, which results in a higher frequency of resistance to P2Y12 inhibitors compared to Caucasians.²⁵⁾ Paradoxically, some reports have shown that P2Y12 inhibition tends to decrease the rate of OKM scale D after FD treatment.²⁶⁾ Although not speculative, these racial differences in the response to P2Y12 inhibitors may have led to the reduction in occlusion rates in this study. The complete occlusion rate of intracranial aneurysms using the Pipeline was 81.4% (n = 1322) in China with a mean follow-up of 8.96 ± 7.5 months²⁷⁾ and 77.4% (n = 47) in South Korea with a mean follow-up of 3 months.²⁸⁾ The complete occlusion rate was 84% at 18 months of follow-up, but the complete occlusion rate after 6 months of treatment was only 55.7% in Hong Kong, indicating that the occlusion rate increases at a slow pace.²⁹⁾ These findings raise the possibility that the repair response to endothelial damage is less likely to occur in Asian patients because of the genetic background. These findings need to be clarified in a multicenter study in Japan.

Cases of image changes due to long-term follow-up

Imaging changes were detected in 6 patients between the first and third years of follow-up. Progressive complete occlusion was achieved in 2 of these 6 patients, which is consistent with previous reports of sustained flow diverting effects in the long term.^{18,30)} A representative case is shown in Fig. 2. In this case, PAO was performed for the contralateral ICA and showed incomplete occlusion until the first year after FD placement. It has been reported that the occlusion rate is reduced when PAO was performed for the contralateral ICA.³¹⁾ After 3 years of long-term follow-up, complete occlusion was achieved. Of the other 4 patients, 1 patient developed in-stent embolus following discontinuation of antiplatelet medication, 1 had complete occlusion with subsequent recurrence, 1 had enlargement after FD implantation, and 1 had gradual occlusion of the FD. We previously reported the case of obstruction in the FD due to discontinuation of antiplatelet agents.¹⁵⁾ Complete occlusion and long-term recurrence may have resulted from the initiation of anticoagulation due to the presence of atrial fibrillation during long-term follow-up (Fig. 3).

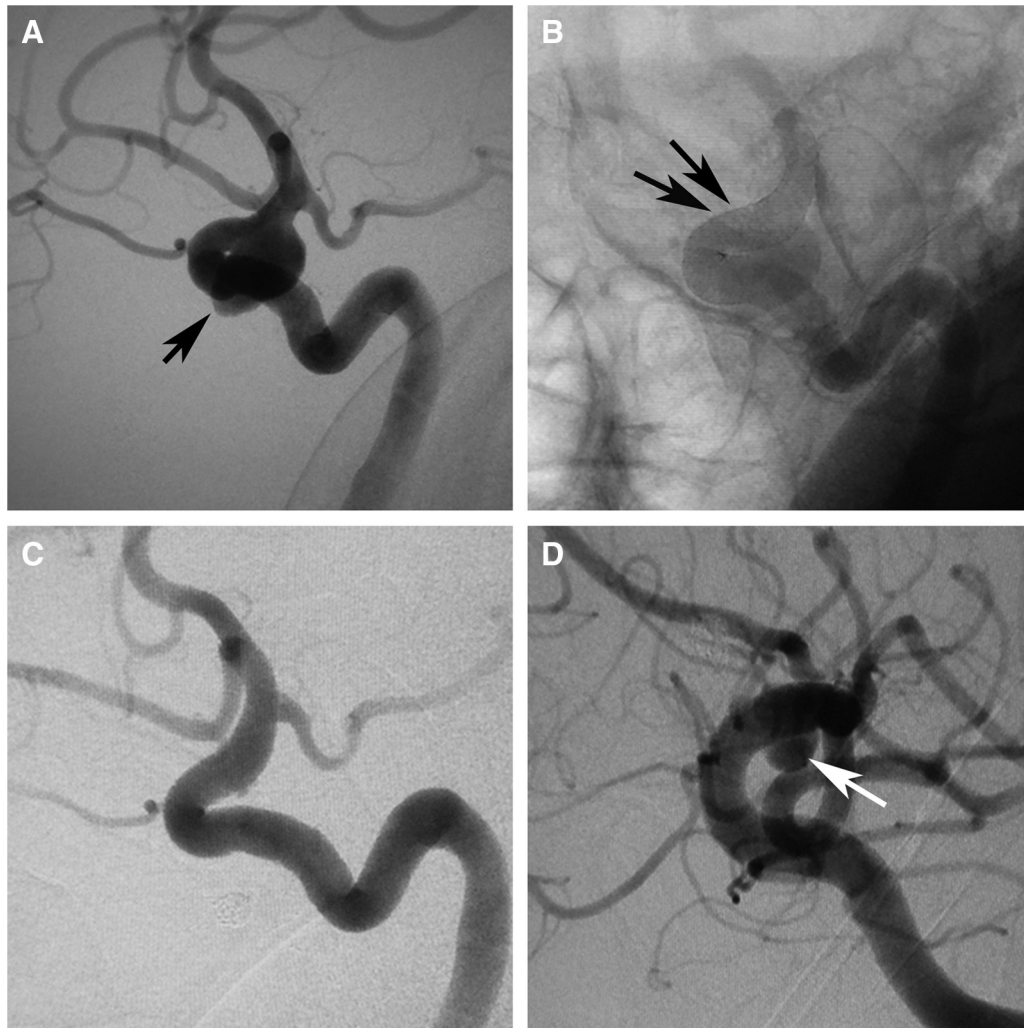


Fig. 3 (A) Left internal carotid angiogram showing a large, irregularly shaped, saccular aneurysm (arrow) with dome size of 11.7 mm and neck size of 6.4 mm located in the C2 segment of the left ICA. (B) A 5 × 20 mm PED was placed (arrows). (C) Angiogram at 1 year later showing complete occlusion of OKM grade D. (D) Anticoagulants were started due to atrial fibrillation, and subsequent angiogram at 3 years showed recanalization of OKM grade B (arrow). ICA: internal carotid artery, OKM: O'Kelly-Marotta, PED: Pipeline embolization device.

We previously reported that anticoagulant medication causes reduced occlusion rate after FD implantation.³²⁾ In particular, atrial fibrillation is a disease that increases with age, so we need to be cautious about anticoagulant therapy. In the present study, 2 patients from the group of patients who had undergone previous anticoagulation therapy were included in the current long-term follow-up group. However, in the current study, the impact of anticoagulant use on cerebral aneurysm occlusion rates and clinical outcomes was not statistically significant.

Enlargement of the cerebral aneurysm occurred even after FD implantation. The aneurysm was thought to result from dissection, and the dome size was giant aneurysm. We performed PAO for

this aneurysm. Progressive occlusion of the implanted vessel after FD placement was associated with difficult FD placement, so the FD was placed in the aneurysm by circling the aneurysm. Careful follow-up may be necessary after such complicated placement methods. Therefore, patients with unusual aneurysms, unusual aneurysm origins, and complicated implantation methods should be carefully monitored for possible changes during long-term follow-up after FD implantation.

Clinical changes in eye symptoms

Interesting results were obtained in terms of extraocular nerve dysfunction and visual pathway dysfunction among the neurological symptoms.

Neurological symptoms of cranial nerves III, IV, and VI, which are related to eye movements, improved in 17 of our 22 patients (77.3%), whereas neurological symptoms of cranial nerve II, which are related to visual function, improved in only 3 of 7 patients (42.8%). Motor neurological symptoms caused by cerebral aneurysms are more likely to improve than sensory neurological symptoms after FD treatment.³³⁾ Long-term improvement of neurological symptoms is an important issue, especially in patients with large and giant cerebral aneurysms, and more detailed and larger studies are needed to clarify the neurological outcomes.

Limitation

In this paper, there are several limitations. One is that there were no cases of rupture of cerebral aneurysm during long-term follow-up after FD implantation in this study, but there were 2 cases of death from unknown causes. The possibility that these patients died due to ruptured cerebral aneurysms cannot be denied. The other limitation of this study is the single-center retrospective design. Cohort studies must be conducted at multicenter in Japan in the future.

Conclusion

Both angiographical and clinical long-term results were good after FD placement for large and giant cerebral aneurysms. Endothelialization of the aneurysmal neck and intra-aneurysmal thrombosis contribute to complete occlusion after FD placement. The primary reason for the somewhat low complete occlusion rate of intracranial aneurysms in Japan may be the generally older patients.

Conflicts of Interest Disclosure

H.O. receives a donation in the form of a research fund to the endowed chair of his departments and about 1 million yen yearly from Medtronic Co., Ltd. The other authors have no conflicts of interest to declare.

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