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SNI: Neurovascular

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Original Article

Safety and efficacy of pipeline embolization device treatments for intradural internal carotid artery aneurysms in a single center in a Japanese population

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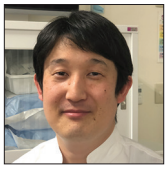

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Received : 28 December 2022
Accepted : 25 February 2023
Published : 17 March 2023

DOI
10.25259/SNI_1165_2022

Quick Response Code:

ABSTRACT

Background: The pipeline embolization device (PED) is the most common flow diverter device in the world. To date, there have been no reports of treatment outcomes specific to intradural internal carotid artery (ICA) aneurysms. The safety and efficacy of the PED treatments for intradural ICA aneurysms are reported.

Methods: 131 patients with 133 aneurysms underwent PED treatments for intradural ICA aneurysms. The mean aneurysm dome size and neck length were 12.7 ± 4.3 mm and 6.1 ± 2.2 mm, respectively. We used adjunctive endosaccular coil embolization for 88 aneurysms (66.2%). A total of 113 aneurysms (85%) were angiographically followed up 6 months following the procedure, and 93 aneurysms (69.9%) were followed up for 1 year.

Results: The angiographic outcome at 6 months showed that 94 (83.2%) aneurysms had O'Kelly-Marotta (OKM) grade D, 6 (5.3%) had C, 10 (8.8%) had B, and 3 (2.7%) had A. At 1 year, 82 (88.2%) aneurysms had OKM grade D, 6 (6.5%) had C, 3 (3.2%) had B, and 2 (2.2%) had A. Multivariate analysis showed that aneurysm neck size and adjunctive coiling were statistically significant in aneurysm occlusion status. Major morbidity modified Rankin Scale >2 and mortality rates related to procedures were 3.0% and 0%, respectively. Delayed aneurysm ruptures were not observed.

Conclusion: These results reveal that PED treatment of intradural ICA aneurysms is safe and efficacious. The combined use of adjunctive coil embolization not only prevents delayed aneurysm ruptures but also contributes to an increase in the rate of complete occlusion.

Keywords: Adjunctive coil embolization, Complete occlusion, Flow diverter, Intradural aneurysms, Pipeline embolization device

INTRODUCTION

A stent collectively called the flow diverter (FD) has been developed and clinically used as an endovascular treatment device for cerebral aneurysms that are difficult to cure using conventional treatment methods.[7,16,21,37,39] The pipeline embolization device (PED) (Covidien/Medtronic, Irvine, CA) is currently the most common FD device in the world and was approved by the Japanese Ministry of Health, Labour and Welfare in April 2015. The targets of treatment were wide-necked cerebral aneurysms with a maximum diameter of ≥10 mm located in the internal

carotid artery (ICA) the petrous segment to the superior hypophyseal segments. However, in August 2020, the upper floor of the ICA and the vertebral artery were added to expand the area of possible locus sites. The adaptation was also expanded to aneurysms with a maximum diameter of ≥5 mm. Regarding the target aneurysms, if an intradural aneurysm ruptures, it causes a subarachnoid hemorrhage (SAH). Such SAHs are known to have poor prognoses. To the best of our knowledge, there have been no reports of treatment outcomes specific to intradural aneurysms. Because the necessity of PED treatment for intradural aneurysms is expected to increase in the future, it is important to evaluate its safety and efficacy. We, therefore, herein report the safety and efficacy of PED treatments for intradural ICA aneurysms in a relatively large Japanese population.

MATERIALS AND METHODS

Case selection

From December 2012 to April 2021, 131 patients with 133 aneurysms underwent PED treatments for intradural ICA aneurysms at our university hospital. A retrospective review of the medical records, outpatient charts, and operative reports was performed. This retrospective study was approved by the Research Ethics Committee, Faculty of Medicine, our University and conducted in accordance with the Declaration of Helsinki (2013).

Antiplatelet therapy

All patients had received dual antiplatelet therapy of 100 mg aspirin and 50–75 mg clopidogrel, per body weight, for at least 10 days before the procedure. Platelet inhibition levels were analyzed on the same day before the procedure or the day preceding the procedure using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA). The reaction units for aspirin and clopidogrel were targeted at <550 and <230, respectively. If the reaction unit did not reach the target values, the doses of the hyporesponsive antiplatelet drugs were increased up to two fold. Recently, 2.5–3.75 mg prasugrel has been used in patients hyporesponsive to clopidogrel. Postoperative antiplatelet therapy was continued up to 6 months following the procedure with the same dose of clopidogrel and 100 mg of aspirin. Based on angiographic results after 6 months, clopidogrel was gradually reduced, and aspirin alone was used. If complete occlusion is confirmed, aspirin can be tapered off within 1–2 years.

PED

In Japan, clinical trials for the Pipeline (Classic) began in December 2012, and the Pipeline Flex (Flex), with its improved delivery system, were approved by the pharmaceutical affairs bodies (Japanese Ministry of Health, Labour and Welfare) in April 2015. In May 2019, the Pipeline Flex with Shield Technology (Shield) was newly approved. The Flex strand is made of 36 cobalt-chromium alloys and 12 platinum-tungsten alloys, and the Shield is made with this strand metal coated with methacryloyloxyethyl phosphorylcholine (MPC) polymer. The MPC polymer inhibits protein adsorption and cell adhesion and is expected to inhibit platelet adhesion and reduce thrombotic complications as well. Neointima formation occurs earlier with Shield than that with Flex, and that the neointima formation shape is concentric, with no hyperplasia, suggesting uniform intima formation.[8] Our institution has been participating in this line of FD development since the clinical trial phase in 2012, and in this case series, the Classic was used for 4 aneurysms, the Flex for 85 aneurysms, and the Shield for 44 aneurysms.

Endovascular procedure

The procedure was performed using the same methods as previously reported; however, after January 2020, the Phenom 27 microcatheter (Medtronic) was used instead of the Marksman microcatheter (Medtronic).[30] Furthermore, after June 2020, the SOFIA SELECT distal access catheter (TERUMO) was used instead of the Navien distal support catheter (Medtronic). If the neck of the aneurysm was not completely covered with a single device, additional PEDs were deployed in a telescoping technique. Furthermore, to prevent delayed aneurysm rupture, we used coils for symptomatic aneurysms, and/or those with, irregular shapes, aneurysm sizes of ≥15 mm, and the jet flow into the sac was associated with a narrow neck. The number of coils used was sufficient to cover the aneurysm wall without aiming for complete occlusion as in conventional coil embolization.

Radiological follow-up procedure

Catheter angiographies were usually performed postoperatively at 6 months and/or 1 year. The degree of aneurysm occlusion was determined by the O'Kelly-Marotta (OKM) grading scale (A: total filling, B: subtotal filling, C: entry remnant, and D: no filling).[27] If the 1-year follow-up angiography showed an OKM grade D without significant in-stent stenosis of ≥50%, according to the Warfarin-Aspirin Symptomatic Intracranial Disease method; thereafter, follow-up with magnetic resonance (MR) angiography was scheduled once a year.[9] Silent 3D time-of-flight MR angiography is a useful radiological modality for anatomical evaluation after FD therapy using PED for intracranial aneurysms.[28] If an OKM grade D could not be confirmed by angiography at the 1-year follow-up, or if significant in-stent stenosis was observed, follow-up angiographies were continued for as long as deemed necessary.

Statistical analysis

All statistical analyses were performed utilizing EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, v2.13.0). Values are expressed as the mean ± standard deviation and range. The differences between the two groups were analyzed by Fisher's exact or χ^2 tests. We performed multivariate logistic regression analysis for aneurysms with an OKM Grade D and the other variables factors for complete occlusion. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical characteristics

Table 1 shows the clinical characteristics of 131 patients with 133 aneurysms treated with PED embolization. Three of 131 patients had bilateral ICA paraclinoid aneurysms. Two patients were treated with the PED and 1 patient with the PED and another FD device. There were 114 unruptured aneurysms initially treated with PED embolization. Eighteen aneurysms recurred after endosaccular coil embolization (11 ruptured and 4 unruptured) or clipping (1 ruptured and 1 unruptured), 1 case of another FD therapy, and 1 aneurysm was a ruptured dissecting aneurysm that was treated with PED embolization after the acute phase. The patients' mean age was 59.1 ± 13.2 years (range 19–83 years), with females accounting for 87.8% (115 patients). The mean aneurysm dome size and neck length were 12.7 ± 4.3 mm and 6.1 ± 2.2 mm, respectively. According to the classification of clinoidal-region ICA aneurysms proposed by Al-Rodhan *et al*. in 1993, the aneurysm locations in the present study were Ia: superior hypophyseal (47 [35.3%]), Ib: ventral paraclinoid (28 [21.1%]), II: ophthalmic (19 [14.3%]), III: carotid cave (12 [9.0%]), and IV: transitional (1 [0.8%]). Furthermore, 12 (9.0%) aneurysms were located in the posterior communicating artery, and 14 (10.5%) aneurysms were unclassifiable.[2] There were 100 asymptomatic, 12 headache only, and 21 symptomatic aneurysms. All the patients with symptomatic aneurysms presented with cranial nerve dysfunction associated with the mass effect of the aneurysms. As many as 110 aneurysms were treated with a single device, and the remaining 23 were treated with multiple devices using the telescoping technique: 21 aneurysms with 2 devices and 2 aneurysms with 3 devices. We also treated 88 aneurysms (66.2%) with adjunctive endosaccular coil embolization.

Radiological outcome

Table 2 shows the angiographic outcome of 133 aneurysms treated with PED embolization. As many as, 113 aneurysms

Table 1: Clinical characteristics of 131 patients with 133 aneurysms.

Parameters	Data
Age, mean±SD, years	59.1±13.2
Sex, female/male (% of females)	115/16 (87.8)
Aneurysm side, right/left	58/75
Aneurysm measurement, mean±SD, mm	
Dome size	12.7±4.3
Neck size	6.1±2.2
Aneurysm morphology, *n* (%)	
Saccular	118 (88.7)
Fusiform	15 (11.3)
Aneurysm location, *n* (%)	
I a: superior hypophyseal	47 (35.3)
I b: ventral paraclinoid	28 (21.1)
II : ophthalmic	19 (14.3)
III : carotid cave	12 (9.0)
IV : transitional	1 (0.8)
Posterior communicating artery	12 (9.0)
Unclassifiable	14 (10.5)
Asymptomatic aneurysms, *n* (%)	100 (75.2)
Headache unrelated to aneurysm, *n* (%)	12 (9.0)
Symptomatic aneurysms, n (%)	21 (15.8)
Visual pathway dysfunction	17 (12.8)
Oculomotor nerve palsy	2 (1.5)
Trigeminal nerve palsy	2 (1.5)
Medical history, *n* (%)	
Hypertension	56 (42.1)
Dyslipidemia	34 (25.6)
Diabetes mellitus	6 (4.5)
Ischemic stroke	5 (3.8)
Hemorrhagic stroke	18 (13.5)
Number of implanted PED devices, *n* (%)	
1	110 (82.7)
2	21 (15.8)
3	2 (1.5)
Adjunctive coil embolization, *n* (%)	88 (66.2)

SD: Standard deviation, PED: Pipeline embolization device, n: Number.

Table 2: Angiographic outcome of 133 aneurysms treated with PED.

Parameters	Data		
Angiographic follow-up, *n* (%)			
6 months	113 (85.0)		
1 year	93 (69.9)		
Latest	115 (86.5)		
OKM scale, *n* (%)	**6 months**	**1 year**	**Latest**
A (Total filling)	3 (2.7)	2 (2.2)	2 (1.7)
B (Subtotal filling)	10 (8.8)	3 (3.2)	5 (4.3)
C (Entry remnant)	6 (5.3)	6 (6.5)	6 (5.2)
D (No filling)	94 (83.2)	82 (88.2)	102 (88.7)

PED: Pipeline embolization device, OKM scale: O'Kelly-Marotta scale, n: Number.

(85%) were angiographically followed up 6 months after the procedure, and 93 aneurysms (69.9%) were followed up 1 year after. Finally, 115 aneurysms (86.5%) were assessed by catheter angiography at either 6 months or 1 year. Angiographic outcome at 6 months showed that 94 (83.2%) aneurysms had OKM Grade D, 6 (5.3%) had C, 10 (8.8%) had B, and 3 (2.7%) had A. At 1 year, 82 (88.2%) aneurysms had OKM Grade D, 6 (6.5%) had C, 3 (3.2%) had B, and 2 (2.2%) had A. The latest angiographic outcome showed OKM Grade D in 102 aneurysms (88.7%), C in 6 (5.2%), B in 5 (4.3%), and A in 2 (1.7%). Univariate and multivariate analyses are shown for age, sex, morphology, aneurysm dome and neck size, number, type, and presence of adjunctive coils [Table 3]. In aneurysm occlusion status, univariate analysis showed age >70 years and the number of implanted PEDs were statistically significant, and multivariate analysis showed aneurysm neck size and adjunctive coiling as statistically significant.

Complications

Major morbidity (modified Rankin Scale, mRS >2) and mortality rates related to these procedures were 3.0% and 0%, respectively. Patients were evaluated by diffusion weighted-imaging (DWI) within 3 days after the procedure. There were 78 aneurysms (58.6%) that showed new high-intensity signals suggestive of microembolic lesions. Symptomatic ischemic complications occurred in 4 patients (3.0%). Two patients suffered a symptomatic stroke immediately following the procedure. DWI on the day of the procedure showed multiple high-intensity signals in the treated area because of distal embolisms and/or parent artery flow insufficiency during the PED deployment. The symptoms of 1 of those patients improved in a short period of time, so the patient was discharged from the hospital. However, the other patient was transferred to another hospital to continue rehabilitation. The other two patients had parent artery occlusions. One had serious symptoms due to sudden PED obstruction the day after the procedure and underwent urgent superficial temporal artery-to-middle cerebral artery (STA-MCA) bypass surgery but was left severely disabled. The other patient had an acute obstruction due to distal parent artery dissection after the PED deployment. That patient also underwent STA-MCA bypass surgery at a later date but was left with serious sequelae. With the exception of these two cases, there were no patients in this case series who had in-stent stenosis of ≥50% or who required retreatment.

Intraparenchymal hemorrhage occurred in one case in which the patient developed a large ipsilateral frontal lobe hematoma on the day following the procedure. The patient had severe hemiplegia and dysphasia but gradually improved and, being able to walk without a cane, was transferred to a rehabilitation hospital. There were no delayed aneurysm ruptures observed in this study.

Although different from the major complications associated with this procedure, a unique complication of delayed hydrocephalus was seen in 2 cases, which has been reported in the literature.[38]

Cranial nerve dysfunction

Regarding the consequences of cranial nerve dysfunction due to the aneurysm's mass effect, in 17 aneurysms of visual pathway dysfunction, symptom improvement was obtained in 4 aneurysms (23.5%), no change in 12 (70.6%), and worsening in 1 (5.9%). Of the 2 aneurysms causing oculomotor nerve palsy, 1 case showed improvement and the

Table 3: Univariate analysis and multivariate analysis of complete and incomplete occlusion for intradural ICA aneurysms treated with PED.

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio	*P*-value	Odds ratio	*P*-value
Age, >70 years	0.08	<0.001	2.25×10^{-16}	0.994
Sex, female	3.62	0.066	4.35×10^{14}	0.995
Morphology, fusiform (control: saccular)	0.41	0.195	0.09	0.226
Aneurysm size				
Dome size (control: 5–9.9 mm)				
10–19.9 mm	2.22	0.493	6.32×10^{7}	0.996
≥20 mm	1.13	0.931	3.05×10^{8}	0.996
Neck size (control: –5.9 mm)				
6–9.9 mm	0.21	0.557	0.02	0.019
≥10 mm	0.21	0.232	0.14	0.336
Number of implanted PED, multi	3.87	0.040	16.5	0.065
PED type, Shield	0.47	0.3	0.23	0.282
Adjunctive coiling	1.30	0.756	24.5	0.037

ICA: Internal carotid artery, PED: Pipeline embolization device

other case had not yet been evaluated. Of the 2 aneurysms causing trigeminal nerve palsy, 1 case showed no change, and the other case had not yet been evaluated.

DISCUSSION

PED treatment

The PED is the most widely used FD stent in the world, and the first prospective PITA trial was reported in 2011, and many studies have been reported there after. PUFS, IntrePED, and ASPIRe have been reported as major studies of PED treatment, and an analysis of these three studies was reported by Kallmes *et al*.[3,14,15,17,25] In their report, the complete occlusion rates after PED treatment were reported to be 75.0% and 85.5% at 180 days and 1 year, respectively. However, a limitation of the PUFS study was the small number of intradural aneurysms. To the best of our knowledge, there are no reports focusing on intradural ICA aneurysms.

Embolic state after PED implantation

In our study, the analysis was limited to intradural ICA aneurysms, and the complete occlusion rates at 6 months and 1 year were 83.2% and 88.2%, respectively, which are more than equivalent to those reported by Kallmes *et al*.[15] However, the occlusion rates for unruptured large and giant aneurysms previously reported from our institution were as low as 64.4% and 72.6%, respectively.[30] That report included 45% C4 and 4% C3 ICA segments, and the results of the treatment of the C4 aneurysms, in particular, may have played a significant role.[30] The low occlusion rate was attributed to the facts that this is a newer technique, performed by surgeons who therefore have less experience with it, and that there is a pharmaceutical law limiting the use of one device per aneurysm. Furthermore, the mean age of the patients in that report was 63.4 years, which tended to be older than the mean age of 56.9–59.9 years in the previous studies.[3,14,17,30] It has been reported that the occlusion rate in elderly patients is low.[1,6,22] In the present study, the patients' mean age was 59.1 years, which was comparable to that in the previously mentioned studies.[3,14,17] However, the group of patients who were ≥70-years-old was significantly less likely to have complete occlusions as revealed in univariate analysis. Another factor that contributed to the high complete occlusion rate in this present study was the use of adjunctive coil embolization.

Bender *et al*. reported that FD treatment with coils accelerates and improves occlusion results without increasing morbidity, with complete occlusion rates as high as 85% at 6 months and 96% at 1 year, respectively.[4] Peschillo *et al*. also reported that complete occlusion was more frequently obtained with coils, 88.9% with coils and 61.5% with PED alone.[31] In a previous report from our institution, only 34% of patients were treated with adjunctive coil embolization, but in the present study, 66.2% of aneurysms were treated with adjunctive coil embolization.[30] In our multivariate analysis, adjunctive coil embolization significantly improved the complete occlusion rate compared to that without coil embolization. For aneurysm occlusion after FD treatment, endothelialization with devices and thrombosis in the aneurysm by flow alternation are important. Although the mechanism of endothelialization has not yet been clarified, we have reported a rare autopsy case in which endothelialization was confirmed after PED treatment at our institution.[29,32] Adjunctive coil embolization may have promoted thrombosis in the aneurysm, which may have resulted in early endothelialization and contributed to the high rate of complete occlusion. It has also been reported that aneurysm size and neck size are important factors for complete occlusion.[11,12] However, in our multivariate analysis, aneurysm size was not significantly related to complete occlusion while neck size was significant. Endothelialization of the neck after PED implantation is crucial for complete occlusion, and the size of the aneurysm may become less relevant when coils are used in combination. However, in Japan, since the PREMIRE study, aneurysms larger than 5 mm have also become a prognostic indication. In that study, coils were used in 3.5% of the cases.[13] In the future, it will be necessary to accumulate more cases to determine whether or not coils should be used for small aneurysms as well.

The effect of the pipeline shield

In the present study, the Shield was used in 44 aneurysms (33.1%). The SHIELD study reported a high occlusion rate and low rates of neurologic morbidity and mortality.[33] *In vivo*, phosphorylcholine surface modified FDs have been shown to inhibit neointimal hyperplasia without reducing aneurysm occlusion rate and have been shown to cause earlier neointimal formation compared to the conventional Flex treatment.[8,23] In our univariate and multivariate analyses, Shield did not contribute significantly to complete occlusion compared to the earlier use of the Classic and the Flex. Of the 44 aneurysms, we were only able to evaluate the occlusion rate by angiography at 1 year in 13 cases; therefore, further accumulation and analysis of cases are necessary.

Complications after PED implantation

In the present study, major morbidity (mRS >2) and mortality rates related to procedures were 3.0% and 0%, respectively. A previous report analysis of three large PED studies showed major morbidity (5.7%) and mortality (4.0%), a meta-analysis reporting overall FD outcomes showed morbidity (5%) and mortality (4%), and another subsequent report showed ischemic complications (4.1%), hemorrhagic

complications (2.9%), neurological sequelae (3.5%), and death (3.4%).[5,7,15] Compared to these reports, our results suggest that the safety of the procedure was satisfactory. It is also noteworthy that we did not find a single case of delayed aneurysm rupture. Delayed aneurysm rupture can be fatal and is the most serious of all complications.[34] In overall FD reports, postoperative aneurysm rupture is seen in 4% of patients, and other reports show varying frequencies ranging from 0% to 6.9%.[5,10,17,18,21,24,35,37] No criteria were established for adjunctive coil embolization. However, Kulcsar *et al*. reviewed 13 cases of delayed aneurysm rupture and proposed four risk factors: large and giant aneurysms, symptomatic aneurysms, saccular aneurysms with a dome-to-neck aspect ratio of >1.6, and inertia-driven flow.[19] Based on this review, we used the adjunctive coil embolization for symptomatic aneurysms of irregular shapes, larger than 15 mm, and/or the jet flow into the sac associated with a narrow neck and were able to completely prevent rupture of delayed aneurysms. There are several reports that the adjunctive coil embolization contributes to the reduction of retreatment and bleeding complications, and our results support this.[20,26,36] On the other hand, delayed hydrocephalus was seen in 2 cases as a unique complication. Teranishi *et al*. cited the size of the aneurysm and the packing density of the coils as factors in its occurrence and reported that the risk of delayed hydrocephalus should be compared with the risk of delayed aneurysm rupture when treating aneurysms with the combination of FD and coil embolization.[38] Neurosurgeons need to be fully aware of the advantages and disadvantages of adjunctive coil embolization.

Change of neurology after PED implantation

It has previously been reported that motor nerve dysfunction tends to improve the neuropathy caused by the mass effect of aneurysms.[30] However, in the present study, motor nerve dysfunction was observed in only two cases because aneurysms in the cavernous sinus region were not included. Most cases were of visual pathway dysfunction. Symptomatic aneurysms were treated with adjunctive coil embolization in all but one case. The overall number of aneurysms treated with adjunctive coil embolization improved in 5, remained unchanged in 12, and worsened in 1 case, suggesting that there was almost no worsening of the mass effect with coils. There is as yet no consensus as to the size of the coil to be inserted for effective prevention of rupture. However, if there are nerve compression symptoms, caution is needed because excessive coil placement may exacerbate the symptoms.

Limitation

The limitation of this study is the single-center retrospective design. This factor must be considered when interpreting the results.

CONCLUSION

Our results show that PED treatment of intradural ICA aneurysms is safe and effective. In addition, the combined use of adjunctive coil embolization not only prevents delayed aneurysm rupture but also contributes to an increase in the high rate of complete aneurysmal occlusions.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

Hidenori Oishi 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.

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How to cite this article: Kitamura T, Fujii T, Yatomi K, Teranishi K, Mitome-Mishima Y, Oishi H. Safety and efficacy of pipeline embolization device treatments for intradural internal carotid artery aneurysms in a single center in a Japanese population. Surg Neurol Int 2023;14:92.