



Treatment Outcomes of 94 Cases of Pipeline Embolization Device in a Single Center: Predictive Factors of Incomplete Aneurysm Occlusion

Ryo Hiramatsu,¹ Ryokichi Yagi,¹ Masahiro Kameda,¹ Naosuke Nonoguchi,¹ Motomasa Furuse,¹ Shinji Kawabata,¹ Hiroyuki Ohnishi,² Shigeru Miyachi,³ and Masahiko Wanibuchi¹

Objective: This study aimed to report the outcome of an endovascular treatment with a pipeline embolization device (PED) at a single center. We also examined the predictive factors for an incomplete occlusion after the PED placement.

Methods: The subjects were 94 patients with 109 aneurysms who underwent the PED placement at our single center from June 2015 to September 2022. As treatment outcomes, we investigated the PED placement success rate, perioperative morbidity and mortality, postoperative cranial nerve improvement rate, and the classification of angiographic result at 6 months after the PED placement. Furthermore, the predictors of an incomplete occlusion were investigated in detail.

Results: One hundred nine aneurysms locations were: C1 (9), C2 (30), C3 (15), C4 (53), and C5 (2) in the internal carotid artery segments. Perioperative morbidity, including the asymptomatic ones, occurred in 10 cases (10.6%). Among these 10 cases, the modified Rankin Scale (mRS) improved to preoperative mRS after 90 days in 9 cases except 1 case. On the other hand, no perioperative mortality was observed. The postoperative cranial nerve improvement rate was 84.4%, and 61.7% of patients had a complete occlusion in the follow-up angiography, 6 months after the PED placement. Predictive factors for an incomplete occlusion after the PED placement were the elderly aged 70 years or older (P -value = 0.0214), the elderly aged 75 years or older (P -value = 0.0009), and the use of anticoagulants (P -value = 0.0388) in an univariate analysis. Further, the multivariate analysis revealed that the elderly aged 75 years or older was a predictive factor of an incomplete occlusion in this study.

Conclusion: We summarized the outcomes of the PED treatment at our single center. In this study, the elderly aged 75 years or older was a predictive factor of an incomplete occlusion after the PED placement.

Keywords: pipeline embolization device, flow diverter, treatment outcomes

¹Department of Neurosurgery and Neuroendovascular Surgery, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka, Japan

²Department of Neurosurgery, Ohnishi Neurological Center, Akashi, Hyogo, Japan

³Department of Neurosurgery, Aichi Medical University, Nagakute, Aichi, Japan

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Corresponding author: Ryo Hiramatsu. Department of Neurosurgery and Neuroendovascular Surgery, Osaka Medical and Pharmaceutical University, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

Email: ryo.hiramatsu@ompu.ac.jp



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Introduction

Although clipping, coiling, and stent-assisted coiling are well-established therapy for the small and medium wide-necked aneurysms, these modalities are limited by an associated morbidity and/or aneurysm recurrence rates.^{1,2)} The advent of flow diverter (FD), such as the pipeline embolization device (PED) (Medtronic, Irvine, CA, USA) has changed the landscape for the intracranial aneurysm treatment by introducing a minimally invasive treatment that could be used to treat wide-necked and large/giant aneurysm effectively.

About eight years have passed since Pipeline Flex (Medtronic, Irvine) was approved in Japan in 2015. In 2019, Pipeline Flex was upgraded to the 3rd generation

Pipeline Flex with Shield technology. The indication for FD in Japan was initially reserved for the wide-necked intracranial aneurysms with a maximum diameter of 10 mm or more located in the internal carotid artery (ICA) proximal to the bifurcation of the posterior communicating artery. Currently, it spreads more widely and targets unruptured cerebral aneurysms with a maximum diameter of 5 mm or more. Adaptation vessels were also extended to the ICA (from petrous to superior hypophyseal segment) and vertebral artery. Furthermore, FRED (Terumo MicroVention) and Surpass Streamline (Stryker) have been approved one after another, and FD has come to be performed at many facilities in Japan. Our center has been treating unruptured cerebral aneurysms using Pipeline Flex since it was approved in Japan in 2015, and we summarized the treatment results of PED at a single center, focusing on the PED placement success rate, perioperative morbidity and mortality, postoperative cranial nerve improvement, and factors involved in an incomplete occlusion in this study.

Materials and Methods

We retrospectively reviewed the medical records, outpatient charts, and operative records of all 94 patients with 109 ICA aneurysms who underwent the PED embolization from June 2015 to September 2022 at Osaka Medical and Pharmaceutical University Hospital. The patients' mean age was 68.1 years (range, 31–89) at the initial treatment and 83 patients (88.3%) were women (**Table 1**). All the patients gave written informed consent for the treatment before the procedures.

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 (Artis zee BA Twin PURE Biplane System, Siemens, Munich, Germany). In almost all cases, a 6-French Flexor Shuttle Guiding Sheath (Cook Medical, Bloomington, IN, USA) was positioned through transfemoral approach as distal as possible in the cervical ICA. A 5-French or 6-French Navien distal support catheter (Medtronic, Irvine) was coaxially advanced as close as the aneurysm neck, and then a Marksman microcatheter (Medtronic, Irvine) or a Phenom microcatheter (Medtronic, Irvine) for the PED delivery was navigated 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 Pipeline size was

determined based on the caliber and length of the parent artery. The Pipeline deployment techniques included a few maneuver combinations including Marksman/Phenom microcatheter unsheathing and pushing and pulling with the catheter system, the Pipeline delivery wire, and the Navien distal support catheter. Additional Pipelines were deployed in a telescoping fashion in the event if the aneurysm neck was not fully covered with a single device. A Dyna CT with diluted contrast agent was used to confirm the full opening of the device and adequate vessel wall apposition. In-stent balloon inflation using HyperForm (Medtronic, Irvine) or Syouryu (Kaneka, Osaka, Japan) balloon catheters is performed in all cases. Regarding indications for PED, we have not performed PED placement for 5–10 mm aneurysms, except for cases with multiple aneurysms. This study was approved by the Ethics Committee of Osaka Medical College (No. 2840).

Antiplatelet therapy

All the patients received dual antiplatelet therapy (DAPT) with a daily dose of 100 mg aspirin (acetylsalicylic acid [ASA]) and 75 mg clopidogrel (CPG) at 7 days before the treatment. Platelet inhibition levels were tested routinely using the VerifyNow (Accumetrics, San Diego, CA, USA) at the treatment with a target reaction unit of <550 for aspirin and <230 for CPG. DAPT was basically continued for 9 months to 1 year after the procedure. If the 6-month follow-up angiography showed a complete aneurysm occlusion without significant in-stent stenosis, DAPT was continued for 3–6 months, then the dose was reduced to ASA or CPG alone, and the single agent was continued.

Follow-up angiography

The follow-up angiography was generally scheduled at 6 months after the treatment. Image evaluation of this angiography was performed using Raymond–Roy occlusion classification.³⁾ When the 6-month follow-up angiography confirmed a complete aneurysm occlusion without significant in-stent stenosis, annual follow-ups with magnetic resonance angiography were scheduled thereafter.

Analysis of factors involved in an incomplete occlusion

Cases evaluated as incomplete occlusion (other than complete occlusion [CO] in the Raymond–Roy occlusion classification) by the follow-up angiography after 6 months were analyzed using an univariate analysis with factors such as sex, age, aneurysm size, smoking, hypertension,

Table 1 Patient background, aneurysm characteristics, and the type of pipeline used

Total cases/Number of aneurysms	94/109 (Total cases)	82/94 (Cases that 6 months follow-up angiography was performed)
Sex		
Female	83 (88.3%)	73
Male	11	9
Age (Y)	68.1 (31–89)	67.0 (31–89)
Symptomatic patients	33 (35.1%)	
Aneurysmal location		
C1	9	7
C2	30	29
C3	15	12
C4	53	45
C5	2	1
Average aneurysmal size (mm)	14.4 (1.8–32.9)	14.1 (2.3–32.9)
Pipeline flex/Pipeline flex with Shield technology	71/66	61/39

Y: Years

diabetes, dyslipidemia, oral anticoagulant use, combined use of coils, multiple cerebral aneurysms, and telescoping or overlapping. Factors predictive at a level of $P < 0.1$ were then evaluated by the multivariate analysis. JMP Pro 15 (SAS Institute Inc., Cary, NC, USA) was used for statistical data processing software, and $P < 0.05$ was considered as statistically significant.

Results

One hundred nine aneurysms locations were: C1 (9), C2 (30), C3 (15), C4 (53), and C5 (2) in ICA segments. The mean aneurysm size was 14.4 (1.8–32.9) mm. There were 33 symptomatic and 61 asymptomatic patients (**Table 1**). All the patients harboring symptomatic aneurysms presented with cranial nerve dysfunction associated with the aneurysm's mass effect. A total of 137 Pipelines were used (mean per patient, 1.5). Seventy-seven patients were treated with a single device and the remaining 16 patients with multiple devices in telescoping or overlapping fashions: 2 devices (9), 3 devices (6), or more (1). Although there were no established criteria for an adjunctive 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, 12 patients (12.8%) were treated with the Pipeline placement and adjunctive coil embolization.

PED placement success rate

A total of 92 out of 94 cases were successful in the first PED placement. Of the two unsuccessful cases, one was a woman with a symptomatic left ICA at the cavernous

portion giant cerebral aneurysm, in which Pipeline Flex and Marksman were tied in the aneurysm. The tied Pipeline Flex and Marksman could not be removed from the 6Fr shuttle sheath, so the femoral artery was dissected and the entire shuttle sheath was removed from the body. At this stage, we have finished the first PED placement. One week after the first PED placement, the second PED placement was performed, and the PED placement was successful by connecting a total of five Pipeline Flexes with a telescoping fashion.⁴⁾ In another case, PED could not be guided to the aneurysm due to tortuousness of the access route, and the FD was changed to FRED for placement.

Perioperative morbidity and mortality

Perioperative morbidity was found in 10 cases (10.8%) including asymptomatic cases. The breakdown was symptomatic intracranial hemorrhage (1), symptomatic cerebral infarction (6), asymptomatic ICA occlusion associated with dissection (1), oculomotor palsy, and puncture trouble (1) (**Table 2**). Among these 10 cases, mRS improved to preoperative mRS after 90 days in 9 cases except 1 case. However, one patient had an asymptomatic right ICA giant cerebral aneurysm at the cavernous portion of ICA, and no compression cranial nerve symptoms due to the aneurysm were observed preoperatively. Postoperative right oculomotor nerve palsy appeared. After that, the patient showed recovery with a steroid infusion and continued oral treatment, but remained. Perioperative mortality was 0% (**Table 2**). Morbidity was evaluated in detail according to age (<65 years, 65–74 years, 75 years and over), and no significant differences were observed among the three groups (P -value = 0.0757) (**Fig. 1**).

Table 2 Perioperative morbidity/mortality by age

	Total cases	By age		
		<65 years	65–74 years	75 years and over
Morbidity				
Symptomatic intracranial hemorrhage	1	1	0	0
Symptomatic cerebral infarction	6	2	0	4
Oculomotor palsy	1	1	0	0
Asymptomatic ICA occlusion associated with dissection	1	1	0	0
Puncture trouble	1	0	0	1
Total	10	5	0	5
Mortality				
	0	0	0	0

ICA: internal carotid artery

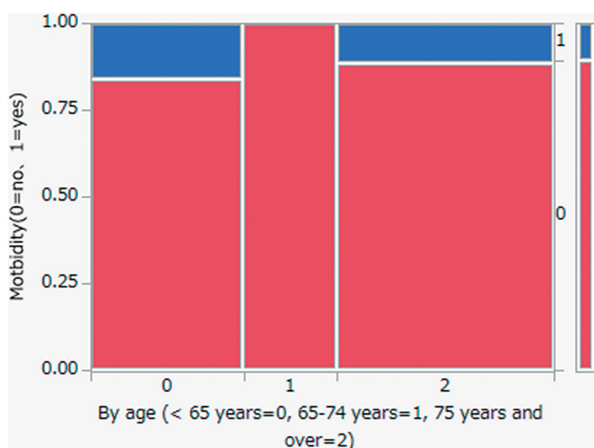


Fig. 1 Morbidity was evaluated in detail according to the age (<65 years, 65–74 years, 75 years and over), and no significant differences were observed among the three groups (*P* value = 0.0757).

Postoperative cranial nerve improvement rate

Thirty-two cases (34.0%) had cranial nerve disorder due to a physical compression by the aneurysm. There were 8 cases of the optic nerve disorder, 7 cases of the oculomotor nerve disorder, 4 cases of the trigeminal nerve disorder, and 24 cases of the abducens nerve disorder, and 9 cases had 1 or more neuropathies. Overall improvement in 27 cases (84.4%), improvement in the optic nerve disorder in 4 cases (50%), improvement in the oculomotor nerve disorder in 6 cases (85.7%), improvement in the trigeminal nerve disorder in 4 cases (100%) and improvement in the abducens nerve disorder in 23 cases (95.8%) was observed.

Embolization rate 6 months after the PED placement/Factors involved in an incomplete occlusion

Six-month follow-up angiography after PED placement was performed in 82 cases with 94 aneurysms of 94 cases with

109 aneurysms. In the evaluation using Raymond–Roy occlusion classification, CO was 58 aneurysms (61.7%), residual neck (RN) was 16 aneurysms (17.0%), and residual aneurysm (RA) was 20 aneurysms (21.3%). Detailed evaluation by age group (<65, 65–74, 75 years and over) revealed that 15 aneurysms (41.7%) had CO, 9 aneurysms (25.0%) had RN and RA was present in 12 aneurysms (33.3%) in the elderly aged 75 years or older (**Table 3**). Factors involved in an incomplete occlusion (other than CO in the Raymond–Roy occlusion classification) were the elderly aged 70 years or older (*P*-value = 0.0214), the elderly aged 75 years or older (*P*-value = 0.0009), and the use of oral anticoagulants (*P*-value = 0.0080) in the univariate analysis. However, no other factors (female, aneurysmal size, smoking, hypertension, diabetes mellitus, dyslipidemia, adjunctive coil embolization, multiple aneurysms, and telescoping or overlapping fashions) predicted an incomplete occlusion in the univariate analysis (**Table 4**). We extracted 4 items, age 70 and older, age 75 and older, smoking, and anticoagulants, which had *P* < 0.1 in the univariate analysis, and evaluated by the multivariate analysis. Multivariate analysis identified the elderly aged 75 years or older (odds ratio [OR] 4.60, 95% confidence interval [CI] 1.07–19.82, *P*-value = 0.04) (**Table 5**). Furthermore, we determined the cut-off age for the CO 6 months after the PED placement using the Receiver Operating Characteristic curve, which was 76 years old (Area Under Curve = 0.677) (**Fig. 2**).

Representative case of incomplete occlusion

A 83-year-old woman underwent a PED placement because multiple aneurysms were found in C3 and C4 of ICA segments. Preoperative 3D-RA showed arteriosclerotic changes before and after the aneurysm (**Fig. 3**). The placement of the pipeline was successful and the patient was

Table 3 Raymond–Roy occlusion classification by age

Raymond–Roy occlusion classification	Number of aneurysms	By age		
		<65 years	65–74 years	75 years and over
Complete obliteration	58	26	17	15
Residual neck	16	4	3	9
Residual aneurysm	20	6	2	12
Total	94	36	22	36

Table 4 Factors involved in an incomplete occlusion (Univariate analysis)

	Number of aneurysms		P-value†
	CO	Incomplete occlusion	
Sex (Female)	50	33	0.4671
Age			
>70 years	26	24	0.0214*
>75 years	15	21	0.0009*
Aneurysmal size			
>25 mm	4	1	0.4127
>15 mm	22	17	0.2831
Smoking	27	10	0.0991
Hypertension	36	26	0.3886
Diabetes mellitus	3	4	0.2574
Dyslipidemia	32	19	0.9964
Anticoagulant	0	4	0.0080*
Adjunct coil embolization	13	4	0.1965
Multiple aneurysms	16	6	0.1078
Telescoping or overlapping fashions	2	2	0.3274

* <0.05. †P-values are expressed as Pearson correlation coefficient. CO: complete occlusion

Table 5 Factors involved in an incomplete occlusion (Multivariate analysis)

	OR	95% CI	P-value
Age			
>70 years	0.72	0.16–3.22	0.66
>75 years	4.60	1.07–19.82	0.04*
Smoking	0.50	0.19–1.40	0.19
Anticoagulant	–	–	0.99

* <0.05.

discharged home without complications. At 6 months follow-up angiography, the C4 aneurysm was assessed as RN and the C3 aneurysm as RA.

Discussion

Since its introduction to the neurointerventional area, FD has revolutionized endovascular therapy of intracranial aneurysms. The PED is FDA approved for treatment of large or giant wide-necked aneurysms along the petrous to superior hypophyseal segment of the ICA. However, over the past years, studies and case series have shown that the PED can successfully treat aneurysms of smaller diameter and beyond the ICA.^{5–10)}

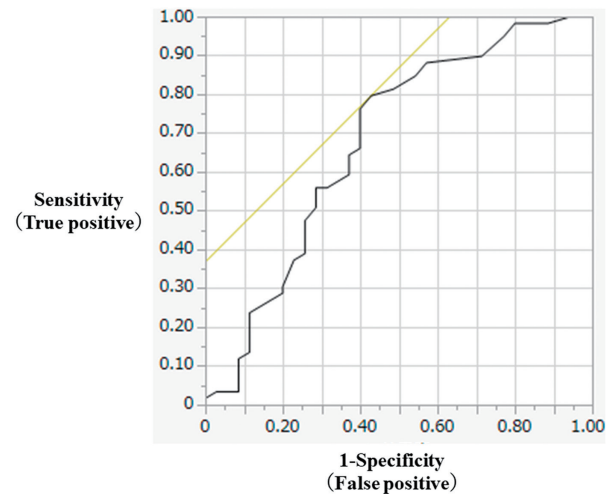


Fig. 2 The cut-off value of age to obtain the CO 6 months after PED placement by the receiver operating characteristic curve was 76 years old (Area under curve = 0.677). CO: complete occlusion

While FD treatment has the great advantage of being highly curative, it has been pointed out that there are cases in which CO did not occur after FD.¹¹⁾ Previous reports have also reported various predictors of an incomplete occlusion after FD, including the patient background (older

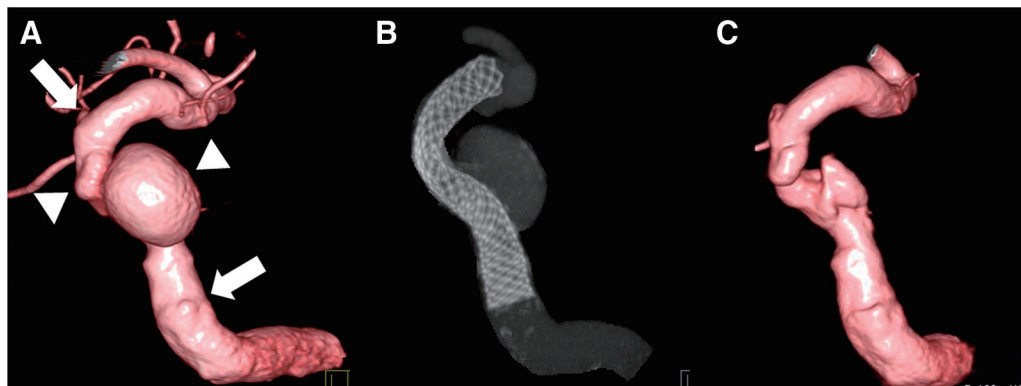


Fig. 3 (A) Preoperative 3-dimensional rotational angiography showed multiple aneurysms at C3 and C4 in ICA segments (white arrowheads), and arteriosclerotic changes before and after them (white arrows). (B) This image is a cone beam CT using a diluted contrast medium performed after the Pipeline placement. (C) Three-dimensional rotational angiography 6 months after the Pipeline placement. ICA: internal carotid artery

than 70 years old^{12,13}), male¹⁴, female¹⁵), aneurysm susceptibility (incorporated branch^{16–18}), on the large curvature¹⁸, fujiform¹⁹, laser-cut stent¹⁹), parameters (low aspect ratio^{19,20}), large size¹⁸, neck diameter >6.46 mm²⁰), and treatment technique (balloon angioplasty¹⁶). In this study, we compared 58 aneurysms diagnosed with an incomplete occlusion and 36 aneurysms evaluated as CO at 6 months after FD. In the univariate analysis, the elderly aged 70 years or older, the elderly aged 75 years or older, and the use of anticoagulants were identified as predictors of incomplete occlusion (P -value = 0.0214, 0.0009, and 0.0080, respectively). Further multivariate analysis revealed that the elderly aged 75 years or older was a predictive factor of an incomplete occlusion in this study. The PED represents an endoluminal device which redirects blood flow away from the aneurysm sac and promotes aneurysm occlusion and parent vessel remodeling over time. CO of aneurysm and vessel wall remodeling are achieved by neointimal formation across the device construct and aneurysm orifice. Atherosclerotic changes in the elderly population may decrease the flow-diverting properties of the device and mostly rely on an aneurysm occlusion though neointimal formation along the device construct is observed. Unfortunately, the re-endothelialization capacity declines with age^{21,22}) resulting in a delayed or incomplete aneurysm occlusion in elderly patients. On the other hand, the univariate analysis showed that oral administration of anticoagulants tended to result in an incomplete occlusion after PED placement in this study. The atrial fibrillation increases with age and is reported to occur in more than 10% of men over the age of 80.²³) Additionally, 40% of patients with an atrial fibrillation are reported to be asymptomatic.²⁴) The main treatment for an asymptomatic atrial fibrillation in the elderly

is the oral administration of anticoagulants, and the number of such patients is expected to increase in Japan in the future. Fujii et al. also reported a tendency for an incomplete occlusion to be observed in patients taking anticoagulants, similar to this study. Oral anticoagulants do not promote thrombus formation due to the stagnation of blood flow after the PED placement, impeding the endothelialization of the aneurysm neck pipeline and leading to an incomplete occlusion.²⁵)

It is a big problem that additional treatment options for FD ineffective cases are limited to additional FD or mother vessel occlusion because the microcatheter cannot be guided into the aneurysm. Therefore, we believe that “target aneurysm retreatment” reported in the PREMIER study of 2.9% at 1-year follow-up and 5.0% at 3-year follow-up⁶) is not acceptable for the FD treatment. Currently in Japan, although the indications for FD have expanded significantly, it is necessary to carefully consider the indications for aneurysms for which coil embolization can be expected to completely cure. Recurrence after the coil embolization can be treated with FD, but we would like to emphasize that the coil embolization cannot be applied to patients with an incomplete occlusion after FD.

This study was limited to a single center and the number of cases was limited.

Conclusion

We have summarized treatment outcomes of 94 cases of the PED in our single center. In this study, the CO cases were as low as 61.7%. The involvement of the elderly was pointed out in the background, and the cutoff value was 76 years old.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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