Pipeline Embolization device for intracranial aneurysms in a large Chinese cohort: factors related to aneurysm occlusion

Bin Luo, Huibin Kang, Hongqi Zhang, Tianxiao Li, Jianmin Liu, Donglei Song, Yuanli Zhao, Sheng Guan, Aisha Maimaitili, Yunyan Wang, Wenfeng Feng, Yang Wang, Jieqing Wan, Guohua Mao, Huaizhang Shi and Xinjian Yang 🄳

Abstract

Background and Purpose: The Pipeline Embolization Device (PED, Covidien/Medtronic) is widely used to treat intracranial aneurysms. This PED in China post-market multi-center registry study (PLUS) investigated safety and effectiveness of the PED for intracranial aneurysms in the Chinese population.

Methods: This was a panoramic, consecutive, real-world cohort registry study. Patients treated with PED with or without coils between November 2014 and October 2019 at 14 centers in China were included, and those treated by parent vessel occlusion or other stents were excluded. Study outcomes included angiographic evaluation of aneurysm occlusion, complications, in-stent stenosis, and predictors of aneurysm occlusion. A central committee reviewed all imaging and endpoint events.

Results: In total, 1171 patients with 1322 intracranial aneurysms were included. The total occlusion rate was 81.4% (787/967) at mean follow-up of 8.96 ± 7.50 months, with 77.1% (380/493) occlusion in the PED alone and 85.9% (407/474) in the PED plus coiling group. On multi-variate analysis, female sex, hyperlipidemia, vertebral aneurysms, PED plus coiling, and blood flow detained to venous phase were significant predictors of aneurysm occlusion. In posterior circulation cohort, there was no variable associated with aneurysm occlusion. In-stent stenosis predictors included current smoking and cerebral sclerosis/stenosis.

Conclusion: In the largest series on PED of multi-center date of China, data suggest that treatment with the flow-diverting PED in intracranial aneurysms was efficacious. The treatment of PED combined coiling and blood flow detained to venous phase after PED implant were associated with aneurysmal occlusion. The occlusion rate of vertebral aneurysms was higher than other location aneurysms.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT03831672.

Keywords: China, intracranial aneurysm, multi-center, occlusion, Pipeline Embolization device, real-world

Received: 22 August 2020; revised manuscript accepted: 30 September 2020.

Correspondence to:
Xinjian Yang
Department of
Interventional
Neuroradiology, Beijing
Neurosurgical Institute
and Beijing Tiantan
Hospital, Capital Medical
University, No.119 South
Fourth Ring West Road,
Fengtai District, Beijing,
100050, China
**yangxinjian@
voiceoftiantan.org**

Bin Luo
Huibin Kang
Beijing Neurosurgical
Institute, Beijing Tiantan
Hospital, Capital Medical
University, Beijing, China

Hongqi Zhang
Xuanwu Hospital, Capital
Medical University, Beijing,
China

Tianxiao Li
Zhengzhou University
People's Hospital,
Zhengzhou, China

Jianmin Liu
Changhai Hospital
Affiliated to Naval Medical
University, Shanghai,
China

Donglei Song
Shanghai Donglei Brain
Hospital, Shanghai, China

Yuanli Zhao
Peking University
International Hospital,
Beijing, China

Sheng Guan
First Affiliated Hospital
of Zhengzhou University,
Zhengzhou, China

Aisha Maimaitili
First Affiliated Hospital
of Xinjiang Medical
University, Urumqi, China

Yunyan Wang
Qilu Hospital of Shandong
University, Jinan, China

Wenfeng Feng
Nanfang Hospital,
Southern Medical
University, Guangzhou,
China

Yang Wang
First Affiliated Hospital
of Nanchang University,
Nanchang, China

Introduction

Flow diverter therapy has gained widespread global acceptance in the treatment of intracranial aneurysms, with overall complete occlusion rates of 75.0–85.5%, and an overall retreatment rate of 3.0%.[1–3] The Pipeline Embolization Device (PED, Covidien/Medtronic, Irvine, CA) is a widely accepted treatment option for patients with intracranial aneurysms, and its efficacy and safety has been demonstrated in many clinical studies.[4–7] However, these studies were assessed on a western population. There is a lack of such large clinical studies in the Chinese population, which are known to have differences in comorbidities

Jieqing Wan
Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Guohua Mao
Second Affiliated Hospital of Nanchang University, Nanchang, China

Huaizhang Shi
First Affiliated Hospital of Harbin Medical University, Harbin, China

including higher rates of internal carotid artery dissection and intracerebral hemorrhage,[8–10] which may affect treatment decisions and outcomes.

The post-market, multi-center, retrospective research on the embolization of intracranial aneurysms with the PED in China (PLUS) registry was a panoramic, consecutive, real-world cohort study designed to assess the safety and effectiveness of PED in embolization of intracranial aneurysms in the Chinese population.

Methods

Because a data sharing statement was not mandatory at the initiation of the study, patients were not asked to share their data. Only individual data that underlie the results reported in the present analysis could be shared. To gain access, proposals should be addressed to the corresponding author.

Study design and participants

All patients with intracranial aneurysms treated with the PED between November 2014 and October 2019 at 14 centers in China were included (including the first PED in Shanghai, China). Local institutional review boards or ethics committees approved the study and the use of patient data. Exclusion criteria were: (a) patients treated by parent vessel occlusion, (b) patients treated by a different stent, and (c) patients lacking 3-dimensional angiographic image(s). Data gathering for the study was performed using electronic data capture. The following information was collected: patient demographics, aneurysm characteristics, antiplatelet regimen, procedure details, complications, and neurological compressive symptoms.

Aneurysms were classified based on the treatment modality used (i.e. PED alone and PED plus with coiling groups) and on the location (i.e. anterior and posterior circulation aneurysm groups).

Procedure details

The use of PED was at the discretion of the treating neuroradiologist at each center. Patients were treated with either the PED Classic or PED Flex. The treatment modality depended on the operators' experience. PED plus coiling was considered in the following conditions: (a) there was a risk of shortening and displacement of PED after release; (b) rapid blood flow at the aneurysmal

neck could be seen from angiography, which was expected to have a high risk of recurrence and postoperative bleeding with FD implantation alone. The brands of coils included Axium™ (Medtronic, Dublin, Ireland), Microplex™ (MicroVention, Aliso Viejo, CA), Target™ (Stryker, Kalamazoo, MI), Orbit™ (Johnson & Johnson, New Brunswick, NJ), Jasper™ (Achieva, Shanghai, China). The duration of dual-antiplatelet therapy differed from 3 to >6 months at each center; a combination of aspirin (100/300 mg daily) and clopidogrel (75 mg daily) was the most common antiplatelet regimen. Patients who were identified as clopidogrel non-responders were administered aspirin (100 mg daily) and ticagrelor (90 mg twice daily). Clinical follow-up was conducted at 3, 6, 12, 24, and 36-months. Aneurysm occlusion was determined using digital subtraction angiography, and grading was established based on two angiographic views using the O'Kelly-Marotta grading scale.[11] The first angiography image follow-up was conducted at 3–6 months after PED implant. For patients who showed complete aneurysm occlusion by angiography follow-up, further angiography follow-up was not routinely performed; for patients who showed incomplete occlusion by angiography follow-up, angiography follow-up was performed up to 24 months or longer. Retreatment was considered for patients who showed incomplete occlusion at the 24-months.

Study outcomes

Study outcomes included angiographic evaluation of aneurysm occlusion, postprocedural thromboembolic or hemorrhagic events, and in-stent stenosis. The status of the parent and covered collateral arteries were also evaluated. Neurological compressive symptoms were evaluated by experienced neurologists and included ambiopia, vision impairment, visual field defect, or dysphagia due to brain stem compression or other symptoms based on imaging and/or assessment of the neurologist. A central review committee comprised three members, including a neurointerventionist, radiologist, and neurosurgeon, reviewed all the imaging and endpoint events. In cases when the evaluation result was disputed, the team reached a unanimous decision after a discussion.

Statistical analysis

Data are presented as means and ranges for continuous variables and as frequencies for

categorical variables. Analysis was carried out using unpaired *t*-tests, chi-squared tests, and Fisher's exact tests.

In each group, univariates analysis was used to test covariates predictive of the following dependent variables: aneurysmal occlusion, in-stent stenosis, and artery stenosis. Interaction and confounding variables were assessed through stratification and relevant expansion covariates. Factors predictive in a univariate analysis ($p < 0.2$) were entered into a multivariate logistic regression analysis.[12] *p*-values < 0.05 were considered statistically significant. Statistical analysis was carried out using SPSS Version 25 (IBM Corp., Armonk, NY, USA).

Results

Sample demographics

A total of 1171 patients with 1322 aneurysms treated in 1319 procedures with PED in 14 centers in China were included. Demographic, baseline, and procedural characteristics of the patients are presented in Table 1. The average age was 53.9 ± 11.4 years, with 69.4% (813/1171) female. Han Chinese accounted for the majority of the population 96.2% (1126/1171). Co-morbidities included hypertension, diabetes, hyperlipidemia, cerebral atherosclerosis, alcohol abuse, and smoking. Aneurysms were incidental in 36.3% (425/1171) of patients, symptomatic in 60.1% (704/1171), and ruptured in 3.8% (45/1171). Among 2.5% (33/1171) of patients who underwent previous treatment, 11 were treated with coiling, 22 with stents-assisted coiling, and 2 with clipping. Of the total patient population, 10.6% (124/1171) of patients were treated in the years 2014–2015, 28.5% (334/1171) in 2016–2017, and 60.9% (713/1171) in 2018–2019. A total of 73.4% (858/1171) underwent angiographic follow-up, with a mean follow-up time of 8.96 ± 7.50 months.

Aneurysm characteristics

Aneurysm characteristics are presented in Table 2. Mean aneurysm size was 12.79 ± 8.75 mm, and the average neck size was 6.21 ± 3.92 mm. There were 83.1% (1099/1322) saccular, 8.2% (109/1322) fusiform, 6.3% (83/1322) dissecting, and 2.3% (31/1322) blister aneurysms. Most of the aneurysms were located in the carotid arteries (83.6%,

1105/1322), 3.6% (48/1322) were in the distal circulation (including middle cerebral artery, anterior cerebral artery, anterior communicating artery, and posterior communicating artery, 10.6% (133/1322) were in the vertebral arteries, and 2.7% were located in basilar and other posterior circulation arteries.

Procedure characteristics

Table 3 shows treatment details and status of collateral and parent arteries. The PED classic and PED Flex were used in similar proportions [45.2% (596/1319) *versus* 54.8% (723/1319), respectively]. Of 1322 total aneurysms, 51.8% (685/1322) of aneurysms were treated with PED alone and 48.3% (637/1322) with PED plus coiling. Among aneurysms treated with PED plus coils, 79.1% (504/637) were loosely packed. Multiple aneurysms were treated with one PED in 13.5% (178/1322) patients. PEDs were deployed successfully in 94.1% (1241/1319) of patients; 5.1% (68/1319) were deployed successfully after adjustment, while 0.8% (10/1319) failed to deploy. The PED covered 927 collateral arteries, of which 67.6% were patent, 5.9% were stenotic, and 2.8% were occluded in the last angiography follow-up. Parent arteries were patent in 91.6% (1211/1322), 7.0% (93/1322) were stenotic, and 1.4% (18/1322) were occluded. Aneurysms treated with PED plus coiling were larger than those treated with PED alone (15.51 ± 8.51 mm *versus* 10.26 ± 8.21 mm, respectively), and aneurysm necks were wider than those treated with PED alone (7.04 ± 3.77 *versus* 5.43 ± 3.91, respectively). Among the aneurysms treated with PED alone, the proportions of fusiform and dissecting aneurysms and the number located in the distal circle of Willis and vertebral artery aneurysm were larger than those treated with PED plus coiling. Rates of periprocedural ischemic complications, subarachnoid hemorrhage (SAH), Intraparenchymal hemorrhage (IPH), and mortality were 7.3% (85/1171), 2.0% (24/1171), 2.0% (23/1171), and 1.5% (17/1171), respectively (Table 3). Of the 230 patients who showed compression symptoms before PED implant, 38.3% (88/230) were treated with PED alone and 61.7% (142/230) with PED plus with coiling. The compression symptoms were improved in 70.5% (62/88) and 22.5% (32/142) of the patients treated with PED alone and PED plus with coiling, respectively.

Table 1. Baseline demographics and clinical characteristics.

Characteristic	Frequency (*n* = 1171)
Female	813 (69.6%)
Mean Age (years)	53.9 ± 11.4
Race	
Han Chinese	1126 (96.2%)
Muslim Chinese	11 (0.9%)
Mongolian	8 (0.7%)
Uygur	12 (1.0%)
Other minority races	14 (1.2%)
Co-morbidities	
Hypertension	397 (33.9%)
Diabetes	63 (5.4%)
Hyperlipidemia	42 (3.6%)
Cerebral atherosclerosis	174 (14.9%)
Alcohol abuse	144 (12.3%)
Smoking	308 (26.3%)
Aneurysm Presentation	
Incidental	425 (36.3%)
Symptomatic	704 (60.1%)
Ruptured (history of SAH)	45 (3.8%)
Baseline mRS	0.62 ± 0.644 (0–5)
Previous treatment	33 (2.8%)
Coiling	11/33 (33.3%)
Stent assistant coiling	22/33 (66.7%)
Clipping	2/33 (6.1%)
Treatment date	
2014–2015	124 (10.6%)
2016–2017	334 (28.5%)
2018–2019	713 (60.9%)

Data are *n* (%), or, when denominator does not equal 1171, *n/N* (%), or mean ± SD (range).
IPH, intraparenchymal hemorrhage; mRS, modified Rankin Scale; PED, Pipeline Embolization Device; SAH, subarachnoid hemorrhage.

Angiographic outcomes

Aneurysmal angiographic follow-up outcomes are presented in Supplemental **Table 1**. A total of 858 patients with 967 aneurysms underwent angiography follow-up, of which 81.4% (787/967) of aneurysms showed complete occlusion. Blister [84.2% (16/19)] and fusiform [69.0% (58/84)] aneurysms had the highest and lowest rates of occlusion, respectively. Aneurysms located in the vertebral [88.5% (92/104)] and basilar [60.9% (14/23)] arteries had the highest and lowest rates of occlusion, respectively. Among ruptured aneurysms, 65.7% (23/35) showed complete occlusion. The occlusion rates of PED Classic and PED Flex were 80.1% (355/443) and 82.4% (432/524), respectively. The occlusion rates in the PED alone and PED plus coiling treatment groups were 77.1% (380/493) and 85.9% (407/474), respectively. The occlusion rate of saccular and fusiform aneurysms and that of carotid, distal circle of Willis, and other posterior circulation was higher in the PED plus coiling group than the PED alone group. The occlusion rate of vertebral aneurysm was higher in PED alone group.

Predictors of occlusion

Of the 967 aneurysms with angiographic follow-up, female ($p = 0.046$), hyperlipidemia ($p = 0.017$), vertebral aneurysms ($p = 0.002$), PED plus coiling ($p < 0.001$), and blood flow detained to venous phase ($p < 0.001$) were predictors of aneurysmal occlusion on multivariate analysis (Supplemental **Table 2**). Age ($p = 0.038$), history of SAH ($p = 0.027$), >6 months dual antiplatelet therapy post-PED implant ($p = 0.005$), aneurysm maximal diameter ($p = 0.015$), and fusiform morphology ($p = 0.005$) were associated with incomplete occlusion on multivariate analysis (Supplemental **Table 2**). For the posterior circulation cohort, there were no variables to compare with.

In the PED alone group, female ($p = 0.003$), vertebral aneurysm ($p < 0.001$), and the blood flow detained to venous phase ($p < 0.001$) were predictors of aneurysmal occlusions on multivariate analysis. More than 6 months dual antiplatelet therapy post-PED implant ($p = 0.002$), aneurysm neck width ($p = 0.011$), and distal Circle of Willis aneurysms ($p = 0.013$) were associated with incomplete occlusion (Supplemental **Table 2**). In the PED plus coiling group, PED Flex ($p = 0.036$), and the blood

Table 2. Aneurysm characteristics.

	PED group	PED plus coiling	*p* value	Total cohort
Number of aneurysms	685 (51.8%)	637 (48.2%)		1322
Aneurysm size (max length, mm)	10.26 ± 8.21	15.51 ± 8.51	<0.0001	12.79 ± 8.75
<10 mm	431 (62.9%)	199 (31.2%)	<0.0001	630 (47.7%)
10–25 mm	213 (31.1%)	342 (53.7%)	0.0003	555 (42.0%)
>25 mm	41 (6.0%)	96 (15.1%)	0.0127	137 (10.3%)
Average neck size (mm)	5.43 ± 3.91	7.04 ± 3.77	<0.0001	6.21 ± 3.92
Ruptured aneurysm	24 (3.5%)	21 (3.3%)	0.816	45 (3.4%)
Parent artery diameter	3.80 ± 0.88	3.97 ± 0.74	0.047	3.88 ± 0.82
Aneurysm Morphology				
Saccular	522 (76.2%)	577 (90.6%)	<0.0001	1099 (83.1%)
Fusiform	80 (11.7%)	29 (4.6%)	<0.0001	109 (8.2%)
Dissecting	63 (9.2%)	20 (3.1%)	<0.0001	83 (6.3%)
Blister	20 (2.9%)	11 (1.7%)	0.2024	31 (2.3%)
Aneurysm Location				
Carotid artery	53 (77.4%)	575 (90.3%)	<0.0001	1105 (83.6%)
Distal Circle of Willis*	31 (4.5%)	17 (2.7%)	0.0774	48 (3.6%)
Vertebral artery	105 (15.3%)	28 (4.4%)	<0.0001	133 (10.1%)
Basilar artery and other posterior circulation†	19 (2.8%)	17 (2.7%)	0.5738	36 (2.7%)

PED, Pipeline Embolization Device.
Data are *n* (%) or mean ± SD.
*Distal Circle of Willis includes the middle cerebral artery, anterior cerebral artery, anterior communicating artery, and posterior communicating artery.
†other posterior circulation includes posterior cerebral artery, posterior inferior cerebellar artery.

flow detained to venous phase ($p=0.011$) were predictors of aneurysmal occlusion, while aneurysm maximal diameter ($p=0.022$) was an independent predictor of incomplete occlusion (Supplemental Table 2). In the posterior circulation cohort, there was no variable associated with aneurysm occlusion (Supplemental Table 2, Figure 1).

Predictors of in-stent stenosis
On multivariate analysis, independent predictors of in-stent stenosis were current smoking status (OR=2.223, $p=0.002$) and cerebral atherosclerosis or stenosis (OR=5.535, $p<0.001$) (OR, odds ratio; Supplemental Table 3).

Discussion
The PLUS study demonstrated the safety and effectiveness of the PED for intracranial aneurysms in the Chinese population, with high rates of complete occlusion and low rates of complications and mortality. Of note, the proportion of PED plus coiling was higher in the PLUS cohort compared with previous studies.[12–14] Also, the PLUS cohort included a large number of off-label

Table 3. Procedure characteristics.

Characteristic	Frequency (*n* = 1322 aneurysms)
PED alone	685/1322 (51.8%)
PED plus coiling	637/1322 (48.2%)
Loose packing	504/637 (79.1%)
Dense packing	133/637 (20.9%)
PED Model	
PED Classic	596/1319 (45.2%)
PED Flex	723/1319 (54.8%)
PED size	
Width (mm)	4.11 ± 0.53
Length (mm)	25.39 ± 5.65
Multiple aneurysms treated with one PED	178/1322 (13.5%)
Patients with multiple PED	75/1322 (5.7%)
Device deployment to target site	
Successful	1241/1319 (94.1%)
Successful after adjustment	68/1319 (5.1%)
Failed	10/1319 (0.8%)
Number of covered collateral arteries	927/1322 (70.1%)
Status of covered collateral arteries	
Patency	627/927 (67.6%)
Stenosis	54/927 (5.9%)
Occlusion	26/927 (2.8%)
Parent artery status	
Patency	1211/1322 (91.6%)
Stenosis	93/1322 (7.0%)
Occlusion	18/1322 (1.4%)
Characteristic	**Frequency (*n* = 1171 patients)**
Blood thinners	
Pre-PED implant dual-antiplatelet therapy >3 days	915/1171 (78.1%)
Post-PED implant dual-antiplatelet therapy >6 months	676/1171 (57.7%)
Angiography follow-up	858/1171 (73.3%)
Mean follow-up time (months)	8.96 ± 7.50
Follow-up distribution	
3 months	250/1171 (21.3%)
6 months	629/1171 (53.7%)

(Continued)

Table 3. (Continued)

Characteristic	Frequency (*n* = 1322 aneurysms)
12 months	211/1171 (18.0%)
24 months	73/1171 (6.2%)
36 months	44/1171 (3.8%)
Periprocedural Complications	
Ischemic complications	85/1171 (7.3%)
SAH	24/1171 (2.0%)
IPH	23/1171 (2.0%)
Mortality	17/1171 (1.5%)
Compression symptoms	230/1171 (19.6%)
PED alone	88/230 (3.5%)
PED plus coiling	142/230 (61.7%)
Improvement of compression symptoms in whole cohort	94/230 (40.9%)
Improvement of compression symptoms in PED alone group	62/88 (70.5%)
Improvement of compression symptoms in PED plus coiling group	32/142 (22.5%)

Data are *n/N* (%) or mean ± SD.
IPH, intraparenchymal hemorrhage; PED, Pipeline Embolization Device; SAH, subarachnoid hemorrhage.
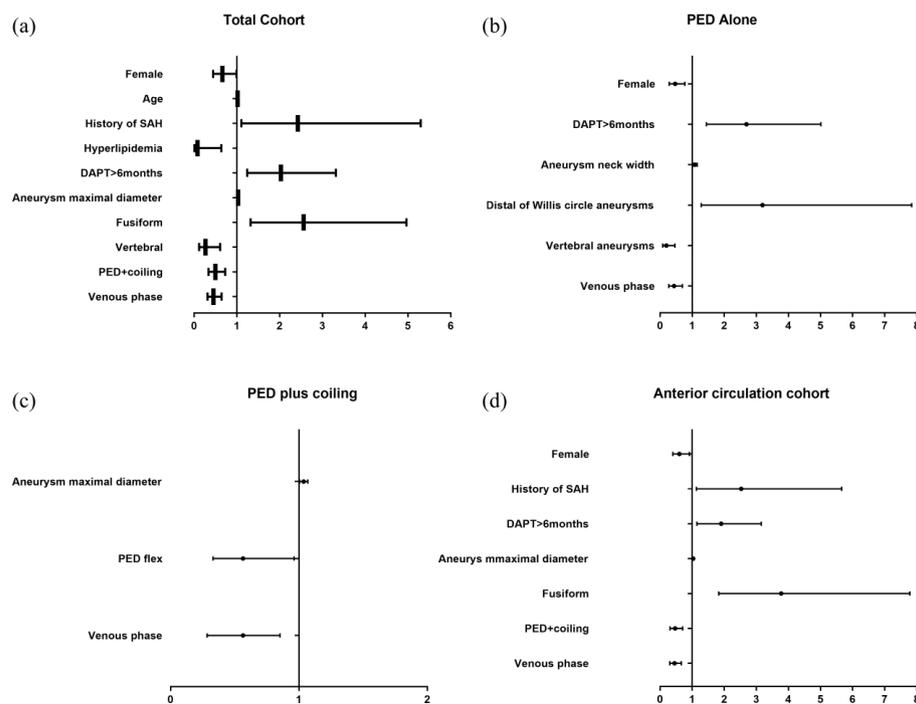
Figure 1. Forest plots demonstrated the predictors for aneurysm occlusion: A, predictors for aneurysm occlusion in total cohort; B, predictors for aneurysm occlusion in PED alone group; C, predictors for aneurysm occlusion in PED plus coiling group; D, predictors for aneurysm occlusion in anterior circulation group.
DAPT, dual-antiplatelet therapy; PED, Pipeline Embolization Device; PED + coiling, PED combined coil treatment; SAH, subarachnoid hemorrhage; Venous phase, blood flow detained to venous phase.

cases (i.e. ruptured aneurysms; fusiform, dissecting, and blister aneurysms; posterior circulation and distal Willis aneurysm) than previous cohort studies,[1,7,15] while the conventional indications for the PED use include wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments.[16]

Aneurysm occlusion rate

The occlusion rate in the present study was comparable with that reported by several studies based on Western populations. For example, in the Pipeline for Uncoilable or Failed Aneurysms (PUFS) study, the complete occlusion rate was reported 86.8% (79/91) at 12 months, in which the PED was used to treat large and giant wide-necked aneurysms of the internal carotid artery.[4] A single-center study of 445 anterior circulation aneurysms treated with PED achieved a complete occlusion rate of 82% at 14 months.[17] In the present study, the occlusion rates increased with the treatment year, presumably due to increased experience, increased number of patients, and the application of PED Flex. While large and small aneurysms had almost the same occlusion rate, it differed among aneurysms of different morphology and of different locations. In addition, the occlusion rate of ruptured aneurysms in our cohort was lower compared with those reported in a meta-analysis of 20 studies that included 223 acutely ruptured intracranial aneurysms treated with flow-diverter stents; the long-term complete/near-complete aneurysm occlusion rate was 88.9% at the mean follow-up of 9.6 months.[18]

Compression symptoms improvement

Szikora *et al.* analyzed compression symptoms in a cohort of 27 patients with 30 aneurysms (>10 mm) treated with flow diversion alone using cross-sectional imaging and clinical follow-up, and of the 17 patients who showed compressive symptoms before treatment, such as vision loss, double vision, and hemiparesis, and 94% (16/17) of patients showed either improvement or complete resolution of symptoms postoperatively.[19] In comparison, in the present study, the compression symptoms were improved in 70.5% and 22.5% of the patients treated with PED alone and PED plus with coiling, respectively. The overall rate of improvement of compression symptoms study was lower, which may be a result of the large proportion of aneurysms treated with PED plus coiling.

Factors associated with aneurysm occlusion

Current clinical evidence regarding factors predictive of aneurysm occlusion after PED placement is conflicting. Bender *et al.* found that adjunctive coiling predicted occlusion, while increasing aneurysm size, incorporated branch vessel, and male sex predicted aneurysm persistence, while prior treatments, vessel of origin, fusiform morphology, and number of devices did not predict aneurysm occlusion.[17] However, fusiform aneurysm morphology was associated with incomplete occlusion in two studies along with other factors, such as decreasing dome-to-neck ratio, the presence of a preexisting laser-cut stent, and shorter angiographic follow-up.[20,21] Adeeb *et al.* found that age >70 years and nonsmoking status independently predicted incomplete occlusion, and suggested lower occlusion rates in the elderly may be related to a deficiency in the endothelial repair pathway, with incomplete endothelization of the stent.[22] Our results corroborate these predictive findings with age, history of SAH, >6 months dual antiplatelet therapy post-PED implant, aneurysm maximal diameter, and fusiform morphology being associated with incomplete occlusion.

Treatment modality: PED alone versus *PED plus coiling.* Whether the flow diverter would absolutely replace coiling embolization in the treatment of intracranial aneurysms is controversial.[23] One reason is that fewer aneurysms are treated with PED plus coiling than PED alone in large studies to be able to compare the two treatment modalities. For example, PED plus coiling was used to treat 0.9% (1/109) in the PUFS trial,[4] and 17.3% (33/191) in the Aneurysm Study of Pipeline in an Observational Registry (ASPIRe) study.[24] A study by Lin *et al.* found that coiling combined with PED can provide a mechanical scaffold to promote endo-saccular thrombosis, although dense packing can cause acute PED thrombotic or compressive symptoms.[13] Comparatively, in the present study, approximately half of the aneurysms were treated with PED plus coiling, which had larger size or a wider neck; however, the occlusion rate of aneurysms was slightly higher in PED plus coiling than PED alone group, and PED plus coiling was found to be a strong predictor of aneurysmal occlusion. Moreover, vertebral aneurysm was a factor associated with occlusion in PED alone group, while not a factor in PED plus coiling group. Based on the present study, PED alone treatment is effective for vertebral artery aneurysms, whereas PED plus coiling

is suitable for large, wide, or fusiform aneurysms. Previous studies have indicated that large and giant aneurysms, fusiform aneurysms, large neck aneurysms, aneurysms with unfavorable size relationship between aneurysm dome, neck, and parent artery are difficult to treat and are associated with many limitations, which can lead to lower rates of complete occlusion; however, aneurysm coiling supported by stenting has been shown to be an effective treatment strategy.[25–29]

Blood flow detained to venous phase. In the present study, the blood flow detained to venous phase was an independent predictor of aneurysmal occlusion in the PED alone group. Brina *et al.* acquired prospective pre- and post-stent implantation four-dimensional phase-contrast magnetic resonance imaging data of 23 patients treated with flow-diverter stents and found flow reduction induced by flow-diverter stent implantation improves aneurysmal thrombosis outcomes.[30]

>6 months dual antiplatelet therapy. Recent studies have reported that <6 months of postoperative dual antiplatelet therapy was associated with ischemic complications;[31,32] however, the effect of >6 months postoperative dual antiplatelet therapy is not clear. In the present study, >6 months of postoperative dual antiplatelet therapy was associated with incomplete occlusion in the total PLUS cohort and in the PED alone group. We deduced that the inhibition of platelet aggregation by long-term dual antiplatelet therapy reduced the thrombosis in the aneurysmal sac. Alternatively, aneurysm occlusion in the PED plus coiling group may have occurred earlier than that in the PED only group, resulting in the earlier discontinuation of therapy.

Aneurysm morphology. In the present study, aneurysmal neck width negatively predicted aneurysm occlusion in the PED alone group, but not in the PED plus coiling group. In aneurysms with large neck width, more blood flow continuously enters the aneurysmal sac, inhibiting occlusion, and PED plus coiling could reduce this blood flow, inducing occlusion of the aneurysms.[25,27,33,34] In addition, in the present study, fusiform morphology was negatively associated with aneurysm occlusion. Complex fusiform morphology often requires more devices or larger or longer constructs for PED deployment that jeopardizes complete stent coverage of the parent artery, contributing to incomplete endothelization and incomplete occlusion.[28,29] In the whole cohort and the anterior circulation aneurysm group, fusiform morphology was the negative factor to aneurysm occlusion in multivariable analysis. While, in the posterior circulation aneurysm group, fusiform morphology was not associated with incomplete aneurysmal occlusion. Moreover, the occlusion rate of vertebral aneurysms in the PED alone cohort was higher than that in the PED plus coiling cohort. We could draw a conclusion that, regarding posterior circulation aneurysm especially vertebral aneurysms, the PED showed a satisfactory treatment effect including fusiform morphology. Importantly, we deduced that fusiform aneurysms in vertebral arteries were different from those in anterior circulations. In vertebral arteries, there was a high proportion of fusiform aneurysms accompanied by type I and II dissecting aneurysms, which had satisfactory outcomes with reconstructive endovascular treatment, while in anterior circulation, the fusiform aneurysms were mostly segmental ectasia or dolichoectatic.[35]

Predictors of in-stent stenosis and artery stenosis

Parent artery reconstruction is an important aspect of aneurysm treatment with PED. In a systematic review of 43 studies with 2448 patients treated with PED, the mean reported rate of in-stent stenosis after PED placement was 8.8%.[36] In a retrospective study of 80 patients treated with the PED, in-stent stenosis was detected in 9.8% (5/51) of patients at a median follow-up of 6 months.[37] In another retrospective study of 139 patients treated with PED, 15.8% of patients showed some degree of in-stent stenosis at a mean follow-up of 6.7 months. Moreover, no aspirin therapy and anterior circulation artery aneurysm location independently predicted in-PED stenosis.[38] In the present study, the rate of stenosis was comparable with those reported in the previous. The parent arteries were patent in 91.6%, 7.0% were stenotic, and 1.4% were occluded. Smoking and cerebral atherosclerosis or stenosis were important factors to predict cerebral atherosclerosis or stenosis, which leads to damage of vessel wall and poor vessel attachment of the PED after PED implantation.

Overall, the present study demonstrated the effectiveness and safety of the PED in the treatment of intracranial aneurysms in Chinese population, with a high rate of complete occlusion and low rate of ischemic and hemorrhagic complications and mortality.

Limitations

Limitations included the retrospective design, potential biases associated with the study design, and variations in patient treatment at different centers. Also, the number of basilar aneurysms treated was small, so the outcomes of univariate and multivariate statistic calculation would be affected.

Conclusion

The PLUS study demonstrated that treatment of intracranial aneurysms with PED in the Chinese population is safe and effective. Female sex, hyperlipidemia, vertebral aneurysms, PED plus coiling, and blood flow detained to venous phase were significant predictors of aneurysm occlusion. In addition, the rate of occlusion of vertebral artery aneurysm is higher for the PED treatment alone group, whereas, PED plus coiling results in a higher rate of occlusion for large, wide, or fusiform aneurysms.

ORCID iD

Xinjian Yang https://orcid.org/0000-0001-7306-0125

Supplemental material

Supplemental material for this article is available online.

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