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Comparison of the Pipeline embolisation device alone or combined with coiling for treatment of different sizes of intracranial aneurysms

Chao Wang ,[1] Bin Luo,[1,2] Tianxiao Li,[3] Aisha Maimaitili,[4] Guohua Mao,[5] Donglei Song,[6] Yunyan Wang,[7] Wenfeng Feng,[8] Yang Wang,[9] Huaizhang Shi,[10] Jieqing Wan,[11] Jianmin Liu,[12] Sheng Guan,[13] Yuanli Zhao,[2] Hongqi Zhang[14]

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CW and BL contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr. Bin Luo;
mamaman@sina.com

ABSTRACT

Objectives The aim of this study was to compare complications and outcomes between intracranial aneurysms treated with the Pipeline embolisation device (PED) alone or with PED combined with coiling for different-sized aneurysms.

Method Patients with aneurysms treated by PED were collected from the PED in China postmarket multicentre registry study. We performed a propensity match analysis to compare the efficacy and safety between PED alone and PED combined with coiling treatment, and then aneurysms were organised into three groups based on their size: small (≤7 mm), medium (≤15 mm to >7 mm) and large/giant (>15 mm). Complications and aneurysm occlusion rates in the aneurysm size groups were compared between PED alone and PED combined with coiling patients.

Result A total of 1171 patients with 1322 aneurysms were included. All patients received clinical follow-up, while angiographic follow-up was available in 967 aneurysms. For small aneurysms, there was no difference in the aneurysm occlusion rate between two groups (79.1% vs 88.4%, respectively), while there was a significant increase in the ischaemic complication rate (8.3% vs 19.3%, respectively, p=0.0001). For medium and large/giant saccular aneurysms, PED combined with coiling significantly improved the occlusion rate (medium aneurysms: 74.7% vs 88.8%, respectively, p<0.0001; large/giant saccular aneurysms: 72.9% vs 86.9%, respectively, p=0.018), while there were no differences in the total complication rate. For large/giant non-saccular aneurysms, two groups showed no differences.

Conclusion Use of the PED with adjunctive coils can significantly improve the occlusion rate of medium aneurysms, without increasing the total complication rate.

Key messages

What is already known on this topic

⇒ The treatment of flow diverters combined with coils could improve the intracanal aneurysms occlusion rate, meanwhile increase the total complication rate, particular in ischaemic complications.

What this study adds

⇒ This study first found that the outcomes of PED combined with coils varied in different size and morphology aneurysm groups. For small aneurysms, PED combined coils did not increase the occlusion rate, while increase the ischaemic complication rate, and for medium and large saccular aneurysms, PED combined with coils improve the occlusion rate without increasing the complication rate.

How this study might affect research, practice or policy

⇒ The medium and large saccular aneurysms are more suitable for PED combined with coils in the endovascular treatment.

INTRODUCTION

The use of flow diverters for treatment of intracranial aneurysms can provide effective clinical outcomes.[1 2] The Pipeline embolisation device (PED; Medtronic, Minneapolis, Minnesota, USA) is a widely used flow diverter that is safe and effective.[3 4] Haemodynamically, the PED diverts blood flow away from the aneurysm, which eventually causes aneurysmal thrombosis and occlusion.[5] Although the PED was designed as a stand-alone treatment, many practitioners prefer to use the PED in combination with coil embolisation, particularly for treatment of complex and giant aneurysms. Based on haemodynamic simulation studies, the addition of coils should reduce both the cavity flow velocity and the wall shear stress, promoting thrombosis formation and aneurysm occlusion.[6] In turn, this should increase the aneurysm occlusion rate and decrease the recurrence compared with the PED alone. However, procedure-related complications, particularly ischaemic ones, are more common.[7 8]

To help improve clinical outcomes, we reviewed our postmarket, multicentre, retrospective register study of embolisation of intracranial aneurysms with PED in China (PLUS (ClinicalTrials.gov identifier: NCT03831672)). The PLUS study was a panoramic, consecutive,

real-world cohort study designed to assess the safety and effectiveness of the PED for embolisation of intracranial aneurysms in the Chinese population.[9] Specifically, we compared the aneurysm occlusion rates and complications between patients treated with the PED alone and those treated with the PED combined with coil embolisation to determine the optimal treatment for aneurysms.

MATERIALS AND METHODS

This study was a subanalysis of the PLUS registry data obtained from a multicentre, observational, international registry of patients treated with a PED. Institutional review boards at each participating centre provided study approval. Patients lacking initial three-dimensional angiographic imaging data and those with parent vessel occlusion were excluded. Patient demographics, treatment history, comorbidities, aneurysm features (type, location and size), procedural details, complications, and clinical and angiographic outcomes were recorded. Patients were grouped and analysed according to treatment (PED alone or PED combined with coiling) and were further subgrouped and analysed based on the aneurysm size.

Outcomes

Clinical follow-up was conducted at 3, 6, 12, 24 and 36 months. Angiographic follow-up was performed at 3–6 months after treatment. Completely occluded aneurysms were then followed up annually, while incompletely occluded aneurysms were followed angiographically for at least 24 months. Aneurysm occlusion was graded according to the O'Kelly–Marotta scale[10]; grade D was defined as complete occlusion and grades A, B and C were defined as incomplete occlusion. Neurological symptoms, complications and events were recorded. Cerebral vasospasm, vascular dissection, in-stent thrombosis on angiography and new cerebral infarction on MRI were defined as ischaemic complications. Delayed aneurysmal rupture and distal intraparenchymal haemorrhage on imaging were defined as haemorrhagic complications. Functional outcomes were assessed using the modified Rankin scale (mRS) at last follow-up. Radiographic results were evaluated by a review committee composed of a neurointerventionist, radiologist and neurosurgeon.

Procedure details

Treatment decisions (PED alone or PED combined with coiling) were made by the operator. In general, the PED with coiling was considered in the following situations: (A) a considerable risk of PED shortening and displacement after release, (B) a high aneurysmal rupture risk (eg, an irregular aneurysm with a daughter sac or a history of sentinel headache) and (C) presentation with subarachnoid haemorrhage following aneurysm rupture (coiling in this context can prevent rehaemorrhage, ensure long-term occlusion and avoid future recurrence).[11] Patients received dual antiplatelet therapy before and after the procedure. Before the procedure, aspirin (100 mg daily) and clopidogrel (75 mg daily) were administered for at least 5 days—doses were adjusted accordingly based on platelet function testing. After the procedure, dual antiplatelet therapy was continued for at least 6 months, followed by use of aspirin alone indefinitely.

All embolisation procedures were performed under general anaesthesia and fully procedural heparinisation. We used triaxial support system to access the aneurysm. The PED device was delivered to the parent artery defect and deployed to cover aneurysmal neck by Marksman microcatheter (Medtronic, Irvine, California, USA). Several endovascular techniques (included use of wires, catheters or balloon angioplasty) would be performed if the device was inadequately expanded. Then coils were subsequently deployed through the previously positioned second microcatheter in aneurysm sac if the operators thought the aneurysm were needed adjunctive coiling.

Statistical analyses

Statistical analyses were performed using RStudio software. Categorical variables are reported as proportions. The data are presented as the mean and range for continuous variables and as frequencies for categorical variables. The analysis was carried out using independent samples t-test (continuous variables) and χ^2 tests (categorical variables) in table 1, and χ^2 tests were used in tables 2 and 3. Preliminary logistic regression was then performed to control for patient age, sex, smoking, aneurysm location, morphology, and maximal diameter, and follow-up duration. Patients were matched by calculated propensity scores using the nearest neighbour method. Matching of the calliper of the propensity score was defined by the precision accuracy (0.1). P values of <0.05 were statistically significant.

RESULTS

Baseline patient and aneurysm characteristics

From November 2014 to October 2019, a total of 1171 patients with 1322 aneurysms were treated using the PED. Patient demographics and clinical characteristics are summarised in online supplemental table 1. Aneurysm characteristics are shown in online supplemental table 2.

Procedures

Procedures, procedure-related complications and clinical outcomes are summarised in online supplemental table 3. The PED Classic and the PED Flex were used in similar proportions (596/1319 aneurysms (45.2%) vs 723/1319 aneurysms (54.8%), respectively). Of the 1322 treated aneurysms, 685 (51.8%) were treated using the PED alone and 637 (48.2%) were treated using the PED combined with coiling. PED placement was successful in 1241/1319 aneurysms (94.1%). Of the remaining aneurysms, 68 (5.1%) were placed successfully after adjustment and 10 (0.8%) failed to deploy. In total, 1319 PEDs were implanted in patients, and one patient harbouring multiple aneurysms treated with single PED in 178 patients, and multiple PEDs treated with an aneurysm in 75 patients. On average, 1.13 PEDs were used per patient.

Table 1 Comparison of the PED alone and PED combined with coiling groups before propensity score matching in the 967 aneurysms with angiographic follow-up

Variable	PED alone	PED combining coils	P value
No. of aneurysms (%)	496	471	
Age (years)	14–82	3–78	
Mean (SD)	53.06 (±11.11)	54.30 (±11.36)	0.084
Female	330 (66.5)	368 (78.1)	<0.001
Comorbidities			
Hypertension	150 (30.2)	168 (35.7)	0.073
Diabetes	19 (3.8)	27 (5.7)	0.165
Hyperlipidaemia	21 (4.2)	14 (3.0)	0.305
Coronary heart disease	28 (5.6)	22 (4.7)	0.494
Alcohol abuse	68 (13.7)	46 (9.8)	0.057
Smoking	140 (28.2)	102 (21.7)	0.018
Aneurysm presentation			0.006
Incidental	262 (52.8)	202 (42.9)	0.002
Symptomatic	217 (43.8)	254 (53.9)	0.002
Ruptured (history of SAH)	17 (3.4)	15 (3.2)	0.833
Pretreatment mRS			0.807
≤2	455 (91.7)	430 (91.3)	
>2	41 (8.3)	41 (8.7)	
Multiple aneurysms	159 (32.1)	133 (28.2)	0.196
Ruptured aneurysms	17 (3.4)	15 (3.2)	0.833
Morphology			<0.001
Saccular	379 (76.4)	430 (91.8)	<0.001
Fusiform	58 (11.7)	24 (4.8)	0.001
Dissecting	47 (9.5)	11 (2.2)	<0.001
Blister	12 (2.4)	6 (1.2)	0.188
Maximal diameter in mm (mean)	9.99 (±7.57)	15.13 (±8.08)	<0.001
≤7 mm	230 (46.4)	86 (18.3)	<0.001
7–15 mm	168 (33.9)	197 (41.8)	0.011
>15 mm	98 (19.7)	188 (39.9)	<0.001
Location			<0.001
Carotid artery	376 (75.8)	419 (89.6)	<0.001
Distal circle of Willis	25 (5.1)	14 (3.0)	0.102
Vertebral artery	82 (16.5)	24 (5.0)	<0.001
Basilar artery and other posterior circulation	13 (2.6)	14 (3.0)	0.740
PED model			0.116
PED Classic	213 (42.9%)	226 (48.0%)	
PED Flex	283 (57.1)	245 (52.0)	
Time to last follow-up imaging (mean)	9.05 (±6.53)	9.01 (±7.59)	0.574
Complete occlusion at last follow-up	382 (77.0)	407 (86.4)	<0.001
mRS score at last follow-up			0.554
≤2	458 (92.3)	430 (91.3)	
>2	38 (7.7)	41 (8.7)	
Complications			
Ischaemic complications	27 (5.4)	58 (12.1)	<0.001

Continued

Table 1 Continued

Variable	PED alone	PED combining coils	P value
Haemorrhagic complications	22 (4.5)	24 (5.1)	0.681
DAR	12 (2.4)	11 (2.3)	0.932
DIPH	10 (2.0)	13 (2.8)	0.448
Compression symptoms	20 (4.0)	31 (6.6)	0.076
Mortality	9 (1.8)	9 (1.9)	0.912

Bold values: p value <0.05.
n (%); p value: χ^2 test.
Median (IQR); p value: t-test.
DAR, delayed aneurysm rupture; DIPH, distal intraparenchymal haemorrhage; mRS, modified Rankin scale; PED, Pipeline embolisation device; SAH, subarachnoid haemorrhage.

Collateral arteries were covered in 927/1322 aneurysms (70.1%). In the 707 patients with angiographic follow-up results, 627/927 aneurysms (67.6%) were patent, 54/927 (5.9%) were stenotic and 26/927 (2.8%) were occluded. The parent artery stenosis and occlusion rates were 93/1322 (7.0%) and 18/1322 (1.4%), respectively.

Complication and clinical outcome data

Any clinical complications were documented for all patients. The PED combined with coiling group had a significantly higher rate of total complications (14.1% vs 9.1%, respectively, p<0.004), which included ischaemic and haemodynamic complications. At last clinical follow-up, the mRS score was ≤2 in 91.0% of patients in the PED alone group and 90.4% of patients in the PED combined with coiling group (p=0.577). Imaging follow-up data were available for 967 aneurysms (73.1%), with a mean follow-up period of 9.0±7.5 months. Of these aneurysms, complete occlusion was achieved in 789 (81.6%), while there was no recurrence. Four hundred and ninety-six of these aneurysms were treated with the PED alone and 471 were treated with the PED combined with coiling. The mean maximal aneurysm diameter was significantly larger in the PED combined with coiling group compared with the PED alone group (15.13 mm vs 9.99 mm, respectively, p<0.001). Furthermore, the complete occlusion rate was significantly higher in the PED combined with coiling group compared with the PED alone group (90.9% vs 74.9%, respectively, p<0.001).

Eighty-five patients (7.3%) experienced a symptomatic ischaemic complication—74 in the perioperative period (44 with cerebral infarction, 30 with transient ischaemic attack or minor stroke) and 11 in the follow-up period (seven with cerebral infarction, four with transient ischaemic attack or minor stroke). Forty-seven patients (4.0%) experienced a haemorrhagic complication—46 in the perioperative period (23 with delayed aneurysmal rupture, 23 with distal intraparenchymal haemorrhage) and one delayed aneurysmal rupture in the follow-up period. The symptomatic mass effect occurred after treatment in 51 patients (4.4%). Eighteen patients died—five from cerebral haemorrhage, six from acute cerebral infarction and seven from other complications. The detailed information was showed in table 1.

Comparison of the PED alone and the PED combined with coiling groups after propensity score matching

Propensity score matching (1:1) to control for age, sex, smoking, aneurysm location and maximal diameter, and follow-up duration resulted in 304 matched pairs. In the propensity score-matched analysis, there were no differences between patients in terms of sex, age or smoking between the PED alone and the PED combined with coiling groups. Furthermore, the two groups had

Table 2 The relation between size and complete occlusion (aneurysms number=967)

Aneurysm size	Total	PED alone	PED coils	P value
≤7 mm	258/316 (81.6)	182/230 (79.1)	76/86 (88.4)	0.059
≤15 mm to >7 mm	300/365 (82.2)	125/168 (74.7)	175/197 (88.8)	<0.0001
>15 mm	231/286 (83.7)	75/98 (76.5)	156/188 (83.0)	0.189
>15 mm (saccular)	162/196 (82.7)	43/59 (72.9)	119/137 (86.9)	0.018
>15 mm (non-saccular)	69/90 (76.7)	32/39 (82.1)	37/51 (72.5)	0.291

Bold values: p value <0.05.
n (%); p value: χ^2 test.
A total of 858 patients with 967 aneurysms underwent angiography follow-up.
PED, Pipeline embolisation device.

Table 3 The relation between size and total complication (ischaemic and haemorrhage complication) (aneurysms number=1322)

Aneurysm size	Total	PED	PED coils	P value
≤7 mm	48/436 (11.0)	27/327 (8.3)	21/109 (19.3)	0.0001
≤15 mm to >7 mm	49/470 (10.4)	19/227 (8.4)	30/243 (12.3)	0.174
>15 mm	55/416 (13.2)	16/129 (12.4)	39/287 (13.6)	0.741
>15 mm (saccular)	40/293 (16.7)	12/71 (16.9)	28/222 (12.6)	0.360
>15 mm (non-saccular)	15/122 (12.3)	4/58 (6.9)	11/64 (17.2)	0.084

Bold values: p value <0.05.
n (%); p value: χ^2 test.
PED, Pipeline embolisation device.

a similar mean follow-up (9.0 vs 8.6 months, respectively), mean maximal aneurysm diameter (11.8 mm vs 13.5 mm, respectively, p=0.387) and aneurysm location and morphology.

The complete occlusion rate was significantly higher in the PED combined with coiling group compared with the PED alone group (89.5% vs 75%, respectively, p<0.001). However, the ischaemic complication rate was also significantly higher in the PED combined with coiling group (11.2% vs 5.9%, respectively, p=0.03). There were no differences in the proportion of patients who experienced other complications, death and an mRS score ≤2 at the last clinical follow-up between the two groups (online supplemental table 4).

Comparison of the PED alone and the PED combined with coiling groups for different aneurysm sizes

Aneurysms were organised into three separate groups based on their sizes—small (≤7 mm), medium (≤15 mm to >7 mm) and large/giant (>15 mm) aneurysms. With respect to complete aneurysm embolisation, there was a similar occlusion rate between the PED alone and the PED combined with coiling groups for small aneurysms (79.1% vs 88.4%, respectively, p=0.059), a higher occlusion rate in the PED combined with coiling group for medium aneurysms (74.7% vs 88.8%, respectively, p<0.001) and a similar complete occlusion rate between the groups for large/giant aneurysms. By further subgrouping the large/giant aneurysms by aneurysm morphology, we found that saccular aneurysms had a higher occlusion rate in the PED combined with coiling group compared with the PED alone group (86.9% vs 72.9%, respectively, p=0.018). Overall, the complete occlusion rate was highest in medium aneurysms treated with the PED combined with coiling, while the complete occlusion rate was lowest in the large/giant aneurysms treated with the PED alone.

For the aneurysm total complications (including ischaemic and haemorrhage complications), there was a higher complication rate in the PED combined with coiling group compared with the PED alone group for small aneurysms (19.3% vs 8.3%, respectively, p=0.0001), but similar total complication rates between the two groups for medium and large/giant aneurysms. Detailed information is shown in tables 2 and 3.

DISCUSSION

The PED is widely accepted for treatment of intracranial aneurysms and its efficacy and safety are well established.[3 12 13] However, numerous studies have reported that the PED has a low long-term occlusion rate for certain types of aneurysms.[14–16] Although the PED combined with coiling was developed to treat aneurysms with an irregular morphology and a high rupture risk, the efficacy and safety of this approach remains unclear. To exclude confounding factors, the present study compared patients treated with the PED alone or with the PED combined with coil embolisation using propensity score matching to control for age, sex, smoking, aneurysm location, size, morphology and follow-up duration. After propensity match analysis, our data yielded complex results that put us into a difficult position; although the rates of complete embolization were significantly higher in the PED combined with coiling group, there was a significant increase in total complications. There are many considerations when using adjunctive coils, including their size, neck width, morphology and location, the aneurysm size is considered most important for clinical outcomes. Thus, we also performed a subanalysis based on aneurysm size (small, medium and large/giant aneurysm groups). For large/giant aneurysms, many studies have reported the benefits of flow diverter adjunctive coils, including improved aneurysm occlusion without any marked increase in aneurysm complications.[17 18] However, the outcomes with use of adjunctive coils for medium aneurysms have not been reported. Importantly, in the present study, PED combined with coiling significantly improved the occlusion rate of medium aneurysms, without increasing the total complications, compared with the PED alone.

Occlusion rates for different aneurysm sizes

The PED was initially developed for treatment of wide-necked complicated and giant aneurysms. Nevertheless, in a study of 100 consecutive patients treated with the PED

for small aneurysms (mean aneurysm size of 5.2 mm), with only two aneurysms treated with adjunctive coils, 85% of patients achieved complete or near-complete embolisation at the final angiographic follow-up.[19] Furthermore, in a prospective study on embolisation of intracranial aneurysms with the pipeline device study of 141 small aneurysms (mean aneurysms size of 5.0 mm), with only five aneurysms treated with adjunctive coils, 106/138 patients (76.8%) achieved complete embolisation at 1 year.[4] We found similar outcomes in the present study, with 183/230 small aneurysms treated with the PED alone showing complete embolisation at final angiographic follow-up and 76/86 small aneurysms treated with the PED and adjunctive coils showing complete embolization (there were no differences in the aneurysmal occlusion rates between the two groups).

Many studies have reported similar findings for large/giant saccular aneurysms. For example, in a study of 44 large/giant carotid aneurysms, complete occlusion was observed in 16/26 patients (61.5%) treated with the PED alone and in 16/18 patients (88.9%) treated with the PED combined with coiling.[17] Furthermore, in a study examining the midterm and long-term follow-up of larger cerebral aneurysms (maximum diameter >15 mm) treated with flow diverter devices only (14 aneurysms) or with flow diverter devices and coils (104 aneurysms) and of small aneurysms treated with a flow diverter only, there were no differences in the complete aneurysm occlusion or subocclusion rates between the groups at final angiography.[20] Comparable results were obtained for large/giant saccular aneurysms in the present study, with higher complete or near-complete occlusion rates in the PED combined with coiling group compared with the PED alone. We also found that the majority of the large/giant non-saccular aneurysms were dissecting or fusiform aneurysms and were located in the posterior circulation. A meta-analysis of 40 giant non-saccular aneurysms treated using the PED reported a long-term complete occlusion rate of only 28% (95% CI 8% to 53%).[21] We found similar occlusion rates for non-saccular large/giant aneurysms between the PED alone and the PED combined with coiling groups.

Few studies have compared the efficacy of the PED alone with the PED combined with coiling for medium aneurysms. A meta-analysis of 2614 patients with small and medium intracranial aneurysms reported a 12-month complete occlusion rate of 74.6% (95% CI 66.8% to 81.7%).[22] In the present study, medium aneurysms had a higher complete occlusion rate when treated with the PED combined with coiling compared with the PED alone. Furthermore, medium aneurysms showed the highest occlusion rate of the different aneurysm size groups. Although the reason for this is likely multifactorial, the relatively smaller size of these aneurysms compared with the large aneurysms may reduce the intra-aneurysmal flow impact, resulting in quicker thrombus formation and a shorter occlusion time. Thus, addition of the coils eventually results in high occlusion rates in the medium aneurysms.

Complications associated with the different aneurysm sizes

In 100 consecutive patients with small aneurysms treated with the PED, Chalouhi *et al*[19] reported symptomatic procedure-related complications in only three patients, with all patients achieving a favourable outcome (mRS score 0–2) at the latest follow-up. Similarly, in the prospective study on embolisation of intracranial aneurysms with the pipeline device (PREMIER) study, the majority of patients exhibited a good prognosis, with only three patients exhibiting a major stroke and one patient with a delayed intracerebral haemorrhage.[4] However, our study found that the PED combined with coiling had a higher major stroke rate, especially of ischaemic stroke, compared with the PED alone. This may be because previous studies had a lower proportion of small aneurysms treated with the PED combined with coiling than in our study (27.2%), which resulted in a lower complication rate. Besides, as the basic volume is too small for implanting adjunctive coils, dense packing can compress the parent artery and reduce blood flow, thus increasing the risk of ischaemic stroke. In a study of 44 large/giant saccular aneurysms, Peschillo *et al*[17] reported similar complication rates between treatment with the PED alone or the PED combined with coiling. Similarly, we found no increase in the total complication rate following treatment with the PED combined with coiling. As previous study presented, larger or giant non-saccular aneurysms showed a higher thromboembolic complications rate and the mortality than the small non-saccular aneurysms.[21 23] In our study, we found that the complications were similar between larger or giant non-saccular aneurysms and small aneurysms, and for the middle aneurysm, our study found the adjunctive coils not escalate the aneurysms complication.

Treatment modality strategy for different sizes of aneurysms

For small aneurysms, we found that use of the PED combined with coiling did not improve the total occlusion rate and actually increased the ischaemic stroke rate, which suggests that addition of coils may not be useful. However, for large saccular aneurysms the addition of coils improved the complete occlusion rate without an increase in ischaemic complications. While for large/giant non-saccular aneurysms, PED combined with coils did not affect the angiographic occlusion and clinical outcomes. Hence, for large/giant non-saccular aneurysms, other factors[9] (such as: stent adherence, incorporated branch vessel, fusiform morphology or presence of a preexisting laser-cut stent) should be fully considered to use of adjunctive coils.

There are also limited studies assessing the use of adjunctive coils for medium aneurysms, and our data suggest that they can significantly improve the aneurysm occlusion rate without increasing the total complication rate compared with the PED alone. Thus, the PED combined with coiling may be a more effective strategy for treatment of medium aneurysms.

Strengths and limitations

The main strengths of this study are its large sample size, real-world cohort design and use of propensity score matching and size subgroup analysis. Potential limitations include the retrospective design and incomplete angiographic follow-up data. Additionally, the short follow-up period and incomplete platelet function testing may have affected the complication and occlusion rates. We are currently planning a prospective study to compare the outcomes of the PED alone or the PED combined with coiling for use in medium aneurysms.

CONCLUSION

PED adjunctive coils can significantly improve the occlusion rate of medium aneurysms without increasing the total complication rate. Further prospective studies are required to confirm these findings.

Author affiliations
[1]Department of Interventional Neuroradiology, Beijing Neurosurgical Institute and Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]Neurosurgery Departement, Peking University International Hospital, Beijing, China
[3]Zhengzhou University People's Hospital, Zhengzhou, Henan Province, China
[4]Department of Neurosurgery, Xinjiang Medical University Affiliated First Hospital, Urumqi, Xinjiang, China
[5]Department of Neurosurgery, Nanchang University Second Affiliated Hospital, Nanchang, Jiangxi, China
[6]Department of Neurosurgery, Shanghai Donglei Brain Hospital, Shanghai, China
[7]Department of Neurosurgery, Qilu Hospital of Shandong University Qingdao, Jinan, Shandong, China
[8]Department of Neurosurgery, Southern Medical University Nanfang Hospital, Guangzhou, Guangdong, China
[9]Department of Neurosurgery, First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[10]Department of Neurosurgery, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
[11]Department of Neurosurgery, Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China
[12]Department of Neurosurgery, Changhai Hospital Affiliated to Naval Medical University, Shanghai, China
[13]Department of Neurointerventional Surgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
[14]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

Contributors Contributors Study concept and design: LB. Acquisition of data and technique support: HZ, TL, AM, GM, DS, WY, FW, YW, HS, WJ, LJ, SG, YZ and BL. Analysis and interpretation of data: CW, BL. Drafting or revising the manuscript: CW. Final approval of the version to be published: BL. Agreement to be accountable for all aspects of the work: CW. Responsible for the overall content: BL.

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ORCID iD
Chao Wang http://orcid.org/0000-0002-9954-5881

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