

Comparison of Flow Diversion and Coiling in Large Unruptured Intracranial Saccular Aneurysms

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Background and Purpose—Flow diversion has emerged as an important tool for the management of intracranial aneurysms. The purpose of this study was to compare flow diversion and traditional embolization strategies in terms of safety, efficacy, and clinical outcomes in patients with unruptured, large saccular aneurysms (≥ 10 mm).

Methods—Forty patients treated with the Pipeline Embolization Device (PED) were matched in a 1:3 fashion with 120 patients treated with coiling based on patient age and aneurysm size. Fusiform and anterior communicating artery aneurysms were eliminated from the analysis. Procedural complications, angiographic results, and clinical outcomes were analyzed and compared.

Results—There were no differences between the 2 groups in terms of patient age, sex, aneurysm size, and aneurysm location. The rate of procedure-related complications did not differ between the PED (7.5%) and the coil group (7.5%; $P=1$). At the latest follow-up, a significantly higher proportion of aneurysms treated with PED (86%) achieved complete obliteration compared with coiled aneurysms (41%; $P<0.001$). In multivariable analysis, coiling was an independent predictor of nonocclusion. Retreatment was necessary in fewer patients in the PED group (2.8%) than the coil group (37%; $P<0.001$). A similar proportion of patients attained a favorable outcome (modified Rankin Scale, 0–2) in the PED group (92%) and in the coil group (94%; $P=0.8$).

Conclusions—The PED provides higher aneurysm occlusion rates than coiling, with no additional morbidity and similar clinical outcomes. These findings suggest that the PED might be a preferred treatment option for large unruptured saccular aneurysms. (*Stroke*. 2013;44:2150-2154.)

Key Words: aneurysm ■ coils ■ flow diverter ■ pipeline embolization device

Endovascular techniques have been gaining ground in the management of intracranial aneurysms. Although coiling was shown to be safe and effective, large aneurysms often fail to achieve complete and durable occlusion, which leaves patients at risk of aneurysm rupture.¹⁻³ Recently, flow diversion has been introduced as an alternative approach to aneurysm treatment.⁴⁻⁶ Flow diverters promote aneurysm occlusion through a process of endoluminal reconstruction of the parent artery and by redirecting blood flow away from the aneurysm sac. The Pipeline Embolization Device (PED) is a dedicated flow diverter that received Food and Drug Administration approval in 2011 for large and giant wide-necked aneurysms of the internal carotid artery. The safety and efficacy of the PED has been demonstrated in several recent series, but most of these series did not include a control group of patients treated with traditional embolization strategies.⁷⁻¹¹ We present the results of the first study comparing PED and coiling in patients with unruptured, large and giant (≥ 10 mm) saccular aneurysms.

Methods

The Jefferson Hospital for Neuroscience Institutional Review Board approval was obtained before data collection. Patients with unruptured, large or giant (≥ 10 mm) aneurysms treated with PED (2011–2012) or coiling (2004–2011) at our institution were identified from a prospectively maintained database. A total of 229 patients, 54 treated with PED and 175 with coiling, were identified. Initial analysis of these patients demonstrated that patients treated with PED were significantly older, had significantly larger aneurysms, and had aneurysms that were more likely to be fusiform in morphology. As there were significant differences between patients treated with PED and coils, fusiform aneurysms (more treated with PED) and anterior communicating artery aneurysms (none treated with PED) were eliminated; no other patients were excluded. Blinded to outcome, 40 PED and 120 coil patients were matched in a 1:3 fashion, respectively, on the basis of patient age and aneurysm size.

Patients undergoing PED therapy received 75 mg/d of clopidogrel and 81 mg/d of aspirin for 10 days before the intervention. Platelet function tests were routinely performed using aspirin assay and P2Y₁₂ assay (VerifyNow; Accumetrics, San Diego, CA) to ascertain that the level of platelet inhibition was between 30% and 90%. Patients with inhibition $<30\%$ were reloaded and the assay was rechecked. Patients found to be poor responders to clopidogrel

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were then switched to Effient. Patients with inhibition >90% were admitted to the hospital, their procedure was canceled, and Plavix was held until platelet inhibition level fell <90%. Treatment was performed with an initial 100-U/kg heparin bolus and maintenance of activated clotting time of 2× the patient's baseline intraoperatively. Heparin was discontinued at the conclusion of the procedure. Dual antiplatelet therapy was continued for ≥6 months after the procedure. Procedures were performed under general endotracheal anesthesia and continuous neurophysiological monitoring, including electroencephalography, somatosensory-evoked potentials, and brain stem auditory-evoked responses. Access was obtained with an 8F femoral sheath, a 6F shuttle sheath (Cook Medical, Bloomington, IN), and a 6F, 070° Neuron catheter (Penumbra, Alameda, CA) or 072 Reverse medical catheter (ev3, Irvine, CA). PEDs were deployed through a Marksman microcatheter (ev3, Irvine, CA) using the triaxial guide-catheter system. The number of stents deployed and the adjunctive use of coils was left to the operator's discretion. The PED procedure was interrupted (ie, no additional devices were placed) when any amount of stasis was seen inside the aneurysm. The expansion of the PED was documented under fluoroscopy or with additional DynaCT/Xpert computed tomography angiography at the operator's discretion. Inadequate vessel wall apposition was remedied with Gateway balloon (Boston Scientific, Fremont, CA) angioplasty when needed. Placement of additional PEDs was considered at follow-up if the aneurysm remained unchanged, despite treatment.

Coiling was performed with an initial 100 U/kg of heparin bolus and maintenance of activated clotting time of 2× the patient's baseline intraoperatively. We generally prefer stent over balloon assistance (because of the flow remodeling effects of stents and the possibility of occluding the neck of the aneurysm) for unruptured wide-necked aneurysms and tend to reserve the balloon remodeling technique only for acutely ruptured aneurysms. When the use of a stent was anticipated, patients were pretreated with daily 81 mg of aspirin and 75 mg of clopidogrel for 10 days before the procedure. Antiplatelet therapy was continued for 2 months after the intervention. Coiling was interrupted when the aneurysm was completely occluded or when no additional coils could be deployed. Stent-assisted coiling was typically performed using the microcatheter jailing technique in which the stent is deployed after the aneurysm is microcatheterized but before coil deployment.

Medical charts were retrospectively reviewed to determine patient demographics, aneurysm characteristics, procedural specifics, and procedural complications. Only clinically relevant procedural complications are reported. Angiographic follow-up (digital subtraction angiography or magnetic resonance angiography) was scheduled at 3 to 6 months, 1 year, 2 years, and 5 years after treatment. Angiographic studies were independently reviewed by 2 authors; aneurysm obliteration rates were determined as percentages and transformed into a dichotomic variable: complete obliteration (100%) and incomplete obliteration (<100%). Regardless of the need for further intervention, any filling at the neck or the dome of the aneurysm was considered <100% occlusion and classified as incomplete obliteration. Clinical outcomes at the last available follow-up were retrospectively collected from follow-up notes of the attending physician and classified using the modified Rankin Scale.

Statistical Analysis

Data are presented as mean and range for continuous variables, and as frequency for categorical variables. Analysis was performed using matched pair analysis as appropriate. Univariate conditional (matched) analysis was used to test covariates predictive of the following dependent variables: treatment complications, follow-up obliteration, and clinical outcome (modified Rankin Scale, 0–2 versus 3–6). Interaction and confounding were assessed through stratification and relevant expansion covariates. Factors predictive in univariate analysis ($P<0.20$)¹² were entered into a multivariate conditional logistic regression analysis. P values of ≤0.05 were considered statistically significant. Statistical analysis was performed with Stata version 10.0 (College Station, TX).

Results

Baseline Characteristics

Mean patient age did not differ between the PED group (60.7±12.7 years) and the coil group (60.3±10.6 years; $P=0.8$). The proportion of female patients was similar between the 2 groups (82.5% in PED, 86% in coil; $P=0.6$). Aneurysm size was 14.9±4.7 mm in the PED group and 14.9±5.9 mm in the coil group ($P=0.9$). Aneurysm neck size did not differ between the PED group (5.0±1.2 mm) and the coil group (4.9±1.7 mm; $P=0.8$). The proportion of aneurysms >15 mm was similar in PED (45%) and coil patients (41%; $P=0.6$). There was no difference between the 2 groups with respect to anterior versus posterior circulation aneurysm location ($P=0.4$) and the overall distribution of aneurysm locations ($P=0.3$). Aneurysm locations are summarized in Table 1.

Aneurysm Treatment

PED procedures were successful in all 40 patients. The number of PEDs used was 1.6±1 per aneurysm. A single PED was used in 27 (67.5%) aneurysms, 2 PEDs in 7 (17.5%), 3 PEDs in 3 (7.5%), 4 PEDs in 2 (5%), and 5 PEDs in 1 (2.5%) aneurysms. Three patients (7.5%) required balloon angioplasty for optimal PED expansion. Four patients (10%) were treated with adjunctive coils (mean, 3.2 coils) in addition to PED. All 4 were treated early in the series, and their aneurysms measured 12, 13, 16, and 22 mm. Of 8 patients with aneurysms ≥20 mm, only 1 had placement of adjunctive coils.

Of 120 patients in the coil group, 67 (56%) were treated with conventional coiling, 52 (43%) with stent-assisted coiling, and 1 (1%) with balloon-assisted coiling. Of these, 70 (58%) had complete aneurysm occlusion (100%) at the end of the procedure.

Procedure-related complications occurred in 3 (7.5%) patients (1 ischemic event, and 1 contralateral and 1 ipsilateral distal hemorrhage) in the PED group and resulted in 1 (2.5%) death (Table 2). In the coil group, there were 9 (7.5%; $P=1$) overall procedure-related complications (8 thromboembolic or ischemic events and 1 cranial nerve palsy). There was no procedure-related mortality in this group. The following factors were tested for as predictors of complications: age, sex, aneurysm location, aneurysm size, aneurysm morphology, and type of treatment. In univariate analysis, older age ($P=0.1$) predicted procedural complications. In multivariate analysis, no factor was a significant predictor of complications even after controlling for the type of treatment.

Table 1. Aneurysm Locations

| Aneurysm Location | PED (%) | Coil (%) |
|-------------------------|-----------|-----------|
| Carotid ophthalmic | 15 (37.5) | 34 (28.3) |
| Carotid cavernous | 8 (20) | 15 (12.5) |
| Vertebrobasilar | 4 (10) | 20 (16.7) |
| Paraclinoid | 9 (22.5) | 29 (24.2) |
| Middle cerebral artery | 1 (2.5) | 7 (5.8) |
| Posterior communicating | 2 (5) | 15 (12.5) |
| Petrous | 1 (2.5) | 0 |
| Total | 40 | 120 |

PED indicates Pipeline Embolization Device.

Clinical Outcome

Clinical follow-up was available for 38 (95%) patients in the PED group and 103 (86%) patients in the coil group. Median follow-up time was 8 months in the PED group and 15 months in the coil group ($P<0.001$). A similar proportion of patients attained a favorable outcome (modified Rankin Scale, 0–2) in the PED group (92%; 35/38) and the coil group (94%, 97/103; $P=0.8$). The 3 patients who had a poor outcome in the PED group include the patient who died from distal parenchymal hemorrhage; the remaining 2 patients had not experienced procedural complications. Two patients in the coil group with a poor outcome at follow-up had experienced procedural complications. The following factors were tested for as predictors of outcome: age, sex, aneurysm location, aneurysm size, aneurysm morphology, type of treatment, and complications. In univariable analysis, increasing aneurysm size ($P=0.1$) predicted a poor clinical outcome (modified Rankin Scale, >2). In multivariable analysis, no factor was a significant predictor of poor clinical outcome.

Angiographic Outcome

Angiographic follow-up was available for 35 (87.5%) patients treated with PED and 90 (75%) patients treated with coiling. Median angiographic follow-up time was 7 months in the PED group and 12 months in the coil group ($P<0.001$). At the latest follow-up, a significantly higher proportion of aneurysms treated with PED (86%; $n=30$) achieved complete obliteration (100%) compared with coiled aneurysms (41%; $n=37$; $P<0.001$; Table 3). Complete aneurysm obliteration was noted in 3 of 3 patients treated with and 27 of 32 (84%) patients treated without adjunctive coils. Retreatment was necessary in fewer patients in the PED group (2.8%; $n=1$) than in the coil group (37%; $n=33$; $P<0.001$). The following factors were tested for as predictors of occlusion: age, sex, aneurysm location, aneurysm size, aneurysm morphology, type of treatment, complications, and follow-up time. In univariable analysis, factors predicting nonocclusion were coiling ($P<0.001$) and older patients ($P=0.2$). In multivariable analysis, coiling (odds ratio, 10.2; 95% confidence interval, 3.0–35; $P<0.001$) was the only statistically significant independent predictor of nonocclusion. There was a trend for older age (odds ratio, 1.4; 95% confidence interval, 1.0–2.0; $P=0.09$) to predict nonocclusion.

Four patients sustained a hemorrhage after aneurysm treatment at a mean of 25 months. All 4 were in the coil group (3.3%; $P=0.2$).

Table 2. Complication and Occlusion Rates Per Aneurysm Size

| | Complications | Complete Occlusion |
|------------------------|---------------|--------------------|
| PED | | |
| Aneurysms 10–19.9 mm | 3/32 (9.4%) | 23/27 (85.2%) |
| Aneurysms ≥ 20 mm | 0/8 | 7/8 (87.5%) |
| Coiling | | |
| Aneurysms 10–19.9 mm | 7/94 (7.4%) | 33/73 (45.2%) |
| Aneurysms ≥ 20 mm | 2/26 (7.7%) | 4/17 (23.5%) |

PED indicates Pipeline Embolization Device.

Discussion

The most important findings of the present study are the following: (1) the PED provides significantly higher occlusion rates of large unruptured saccular aneurysms than coiling; (2) the PED significantly reduces the need for retreatment of large unruptured aneurysms; (3) treatment with PED can be undertaken with a similar rate of morbidity compared with coiling; and (4) short-term clinical outcomes do not seem to differ between patients treated with PED and coiling.

The PED has emerged as an important treatment strategy for intracranial aneurysms and has received considerable attention in the recent literature. The device was initially reserved for large and giant aneurysms, but smaller and morphologically less complex aneurysms are increasingly treated with the PED.¹³ The best treatment option for intracranial aneurysms, however, is the subject of vigorous debate, as many investigators have raised concerns about the morbidity rate associated with flow diverters.¹⁴ In the Canadian experience, O'Kelly et al¹⁵ treated 97 aneurysms with the PED and reported a combined morbidity and mortality rate of 10.7% (6.3% mortality, 4.4% morbidity). They concluded that the morbidity of this treatment must be considered in the context of available alternative embolization strategies. Chitale et al⁷ treated 42 aneurysms with the PED and reported postoperative complications in 13.9% of patients. Likewise, in a multicenter study that included 56 patients treated with PED, Kan et al¹⁶ reported 6 periprocedural thromboembolic events and 4 fatal postprocedural hemorrhages for a major complication rate of 8.5%. A recent meta-analysis of 29 studies, including 1451 patients with 1654 aneurysms, found that the rate of procedure-related morbidity and mortality with flow diverters was 5% and 4%, respectively.¹⁷ The authors concluded that the risk of procedure-related morbidity and mortality is not negligible and should be taken into account when considering the best therapeutic option for intracranial aneurysms. Elsewhere, however, the morbidity rate associated with the PED was found to be negligible.^{8,10} As such, Saatci et al¹⁰ reported remarkably low rates of mortality (0.5%) and permanent morbidity (1%) in a large series of 191 patients with 251 aneurysms. Likewise, Pistocchi et al⁵ treated 30 aneurysms at and beyond the circle of Willis with a permanent neurological morbidity rate of only 3.7% and no mortality. Moreover, some investigators, based on findings from noncontrolled studies, have recommended that the PED be used as a first-line option for intracranial aneurysms. Yu et al¹⁸ recently reported the results of a prospective nonrandomized multicenter study of 143 patients with 178 aneurysms. The rate of periprocedural death or major stroke was 3.5%, the rate of minor neurological complications within 30 days was 3.5%, and the rate of complete aneurysm occlusion was 84%. Although the study lacked a control group,

Table 3. Rates of Aneurysm Occlusion

| | Complete Aneurysm Occlusion | | |
|---------|-----------------------------|-------------|------------|
| | ≤ 6 mo | 7 to 12 mo | >12 mo |
| PED | 24/28 (86%) | 12/14 (86%) | 1/1 (100%) |
| Coiling | 11/29 (38%) | 22/43 (51%) | 9/32 (28%) |

PED indicates Pipeline Embolization Device.

the authors concluded that the PED should be considered a first choice for treating unruptured aneurysms and recurrent aneurysms after previous treatments. This variation in opinion and practice highlights the need for studies comparing flow diversion with conventional endovascular strategies. To our knowledge, only 1 study has provided a direct comparison of flow diversion and traditional embolization strategies. In this small study by Lanzino et al,¹⁹ 21 patients with 22 paraclinoid aneurysms treated with the PED were matched with historic controls (coiled aneurysms) of similar size and location. The authors reported a significantly higher rate of complete occlusion in PED patients (76%) than in coiled patients (21%) with a similar rate of morbidity and concluded that long-term follow-up was important to validate flow diversion definitively as a superior therapeutic strategy for proximal internal carotid artery aneurysms. In the current study, we provide evidence that for unruptured large aneurysms, the PED provides higher occlusion rates than traditional embolization strategies with similar rates of morbidity/favorable outcomes. Our data could also suggest that adjunctive coiling may not be needed with flow diverters, as 84% of aneurysms achieved complete obliteration without adjunctive coiling.

Distal intraparenchymal hemorrhage is the most dreaded complication of flow diversion. This complication occurred in 2 patients treated with flow diverters versus none of the coiled patients in the present study. The cause of distal parenchymal hemorrhage is not completely understood but possible mechanisms include hemorrhagic conversion of ischemic infarcts or postflow diversion hyperperfusion phenomenon. A recent study suggested that high levels of platelet inhibition were associated with hemorrhagic complications after treatment with flow diverters.²⁰ Although delayed aneurysm rupture has been previously reported with PED,²¹ no patient experienced this complication in the current study. Moreover, all 4 patients who experienced delayed aneurysm rupture were in the coil group, which suggests that the PED may even provide more reliable protection against aneurysm rupture than conventional endovascular techniques. Larger studies with longer follow-up periods, however, are needed to confirm this finding. Although thromboembolic events are theoretically more likely to occur during PED procedures because of the size of delivery devices and the frequent use of multiple stents of high metal surface area coverage, this study found no difference in ischemic and thrombotic events between PED patients and coiled patients.

The main limitation of coiling in large and giant aneurysms is the risk of aneurysm recurrence.¹⁻³ In a systematic review of giant aneurysms treated with endosaccular coiling, aneurysm recanalization was found to occur in >50% of aneurysms.²² The use of balloon and stent technology was shown to improve treatment durability but results remain suboptimal.²³ In the current study, 59% of coiled aneurysms failed to achieve complete occlusion at follow-up and as many as 37% required further intervention. This stands in stark contrast with the 86% rate of complete occlusion and the 2.8% rate of retreatment in patients treated with PED. The relatively high rate of complete aneurysm occlusion with PED in our study is in line with the findings of recent series. Complete occlusion was noted in 63% of aneurysms in the study by Kan et al,¹⁶ 73.6% of

aneurysms in the Pipeline for Uncoilable or Failed Aneurysms (PUFS) study,²⁴ 82.6% of aneurysms in the study by Pistocchi et al,⁵ and 95% of aneurysms in the study by Lylyk et al.⁸ Overall, the PED significantly improves angiographic outcomes in patients with large unruptured aneurysms.

The limitations of this study are related to its retrospective design and absence of randomization. Angiographic follow-up was not available for 12.5% of PED patients and 25% of coil patients. Also, the 2 groups were not comparable with respect to angiographic follow-up time. The shorter follow-up time in the PED group, however, further supports the efficacy of the PED because the occlusion rate of aneurysms treated with flow diverters increases with time.^{8,18} It should also be noted that the occlusion rate of aneurysms treated with coils decreases with time, which may have favored the PED group. The lower retreatment rate with the PED may be partly related to the fact that retreatment is usually limited to placement of further PEDs and consequently one tends to observe for longer periods with flow diverters. The influence of this factor, however, is very limited because only 5 patients treated with PED did not achieve complete aneurysm occlusion at follow-up (and 4 showed significant reduction in size). This study did not compare the PED with parent vessel sacrifice, another endovascular alternative for large and giant aneurysms. For some authors, parent vessel sacrifice even remains the preferred modality in this setting.¹⁴ This study mainly reports on short-term clinical outcomes of PED treatment. Because of better anatomic result, the PED could probably provide better long-term outcome than coiling, but this remains to be proven conclusively. Finally, because aneurysms in the coil group were treated earlier during the study period, increased operator experience may have somewhat favored the PED group. Despite these limitations, our study provides the first comparative analysis of PED and coiling in patients with large unruptured saccular aneurysms.

Conclusions

In this study, we compared the PED and coiling in terms of safety, efficacy, and clinical outcomes in patients with large unruptured aneurysms. We found that the PED provides higher aneurysm occlusion rates than coiling with lower retreatment rates. Importantly, procedural morbidity and short-term clinical outcomes are comparable between the 2 treatment modalities. These findings suggest that the PED might be a preferred treatment option for large unruptured saccular aneurysms.

Disclosures

None.

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