Pipeline embolization device for recurrence of previously treated aneurysms

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OBJECTIVE The utilization of the Pipeline embolization device (PED) has increased significantly since its inception and original approval for use in large, broad-necked aneurysms of the internal carotid artery. While microsurgical clipping and advances in endovascular techniques have improved overall efficacy in achieving complete occlusion, recurrences still occur, and the best modality for retreatment remains controversial. Despite its efficacy in this setting, the role of PED utilization in the setting of recurrent aneurysms has not yet been well defined. This study was designed to assess the safety and efficacy of PED in the recurrence of previously treated aneurysms.

METHODS The authors reviewed a total of 13 cases in which patients underwent secondary placement of a PED for aneurysm recurrence following prior treatment with another modality. The PEDs were used to treat aneurysm recurrence or residual following endovascular coiling in 7 cases, flow diversion in 2, and microsurgical clipping in 4. The mean time between initial treatment and retreatment with a PED was 28.1 months, 12 months, and 88.7 months, respectively. Clinical outcomes, including complications and modified Rankin Scale (mRS) scores, and angiographic evidence of complete occlusion were tabulated for each treatment group.

RESULTS All PEDs were successfully placed without periprocedural complications. The rate of complete occlusion was 80% at 6 months after PED placement and 100% at 12 months in these patients who underwent PED placement following failed endovascular coiling; there were no adverse clinical sequelae at a mean follow-up of 26.1 months. In the 2 cases in which PEDs were placed for treatment of residual aneurysms following prior flow diversion, 1 patient demonstrated asymptomatic vessel occlusion at 6 months, and the other exhibited complete aneurysm occlusion at 12 months. In patients with aneurysm recurrence following prior microsurgical clipping, the rate of complete occlusion was 100% at 6 and 12 months, with no adverse sequelae noted at a mean clinical follow-up of 27.7 months.

CONCLUSIONS The treatment of recurrent aneurysms with the PED following previous endovascular coiling, flow diversion, or microsurgical clipping is associated with a high rate of complete occlusion and minimal morbidity.

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KEY WORDS intracranial aneurysm; recurrence; flow diversion

THE treatment of intracranial aneurysms has increasingly shifted away from open microsurgery as endovascular techniques and technologies have continued to improve. The introduction of flow diversion marked another major paradigm shift in the neurosurgical treatment of intracranial aneurysms. Initially approved for the treatment of large, broad-necked aneurysms of the petrous to supraclinoid internal carotid artery (ICA),^{2,21} utilization of the Pipeline embolization device (PED, Covidien/ev3) has been described in numerous other locations

and aneurysm subtypes. In addition to treatment of unruptured large, broad-necked aneurysms, several studies have evaluated the use of PEDs in the treatment of aneurysm recurrence following prior treatment with endovascular or open microsurgical modalities.

One of the greatest pitfalls in the treatment of intracranial aneurysms with standard coils or stent-assisted coiling is the high recurrence rate, with recurrence rates of 13%–48% and retreatment in up to 13% of previously coiled aneurysms.^{4,13,24} Microsurgical clipping is largely regarded as

ABBREVIATIONS ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PED = Pipeline embolization device; PRU = platelet reactivity unit; SAH = subarachnoid hemorrhage.

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the most robust option, resulting in complete obliteration in up to 87% of cases and a retreatment rate of around 4.5%.²⁴ While microsurgical clipping certainly provides a more durable result, aneurysm recurrence following clipping is associated with a substantial hemorrhage rate of 50%.²³ Debate as to the best treatment modality following recurrence of a previously treated aneurysm certainly exists, although the low morbidity and reconstructive potential of the PED have produced an intriguing option.

The PED was designed as a flexible low-porosity endoluminal stent with the ability to reduce hemodynamic flow between the parent artery and aneurysm, promoting aneurysm thrombosis, allowing flow to branch arteries, and providing a scaffold for intimal overgrowth. This reconstructive potential, low associated morbidity and high efficacy in achieving aneurysm occlusion has garnered substantial popularity for this treatment modality. With complete obliteration of 86% and retreatment only seen in 2.8% of patients, PED outcomes are similar to those observed in microsurgical clipping and significantly improved in comparison with other endovascular therapies.⁶ Despite the highly efficacious results, the role of PED utilization in the setting of recurrent aneurysms has not yet been well defined. This study assesses the safety and efficacy of PED as a second-line treatment for aneurysm recurrence following endovascular or microsurgical treatment.

Methods

Patient Population

Institutional review board approval was obtained for the study protocol. Patients with intracranial aneurysms treated with the PED between July 2011 and November 2016 at a single institution were reviewed. Thirteen patients with previously treated aneurysms that were secondarily treated with a PED were retrospectively identified. PED treatment is routinely offered to patients with complex, large, wide-necked aneurysms of the ICA from the petrous through the supraclinoid segment. Baseline patient, aneurysm, and procedural characteristics were recorded.

Procedure

At least 7 days prior to intervention, patients were started on 75 mg clopidogrel and 325 mg aspirin daily. Baseline preprocedural platelet reactivity unit (PRU) values were assessed. Platelet function tests were performed for all patients using a P2Y12 assay (VerifyNow, Accumetrics), and the PED procedure was performed if the PRU value was within the therapeutic window (60–240).¹⁰ During the procedure, an initial bolus of heparin was administered, and the activated clotting time was maintained at at least twice the patient's baseline level. Following the procedure, heparin was discontinued, but the treatment was not pharmacologically reversed. Patients were maintained on dual-antiplatelet therapy for at least 3 months, and aspirin therapy was continued indefinitely.

PED placement was performed under general anesthesia. Angiography was obtained to assess the dimensions of the recurrent aneurysm and to appropriately size the PED

to the width of the inflow vessel to avoid any endoleak. Femoral artery access was obtained with a 6-Fr introducer sheath. A triaxial system was used, with a 6-Fr shuttle sheath (Cook Medical) placed in the cervical segment of the vessel proximal to the intracranial vessel of interest, followed by a 0.072-inch (inner diameter) Navien catheter (Covidien/ev3). Finally, a Marksman microcatheter (Covidien/ev3) was advanced over a Traxcess microwire (MicroVention) until adequate placement at the distal landing zone, and the PED was then deployed. This triaxial system was routinely used for PED deployment to maximize support during forward loading of the system. PED deployment was performed under angiographic surveillance, and postdeployment angiography confirmed adequate placement across the aneurysm neck and documented patency of the intracranial vasculature. The number of stents was left to the operator's discretion, although the use of multiple stents is typically reserved for fusiform aneurysms or a malpositioned device. Patients were evaluated overnight in the neurocritical care unit for any periprocedural complications.

Outcomes

All patients had at least 6 months of follow-up. All procedural and postprocedural complications were documented. Delayed complications and clinical outcomes were recorded during follow-up, at 1, 6, and 12 months after PED placement. Clinical outcomes were assessed based on modified Rankin Scale (mRS) scores, and the score obtained at the most recent clinical follow-up visit was used for analysis. Angiographic outcomes were assessed between 3 and 6 months following the procedure and then again at 1 and 3 years. Aneurysm occlusion was classified as complete (Raymond 1), partial (Raymond 2), or incomplete (Raymond 3).

Results

Patient Characteristics

The mean age of the patients was 46.9 years (range 12–71 years, Table 1). Seven patients were male (53.8%), and 6 were female (46.2%). The mean aneurysm size was 7.5 mm (range 2.0–25.0 mm). Aneurysm morphology included saccular (n = 9), blister (n = 1), and fusiform (n = 4). One patient harbored 2 recurrent aneurysms, which were treated with a single PED. Aneurysm locations involved the carotid ophthalmic (n = 5), paraclinoid carotid (n = 3), posterior communicating (n = 2), anterior choroidal (n = 1), cavernous carotid (n = 1), petrous carotid (n = 1), and middle cerebral (n = 1) arteries.

Treatment

Seven patients had undergone primary endovascular coiling in their initial procedure. Four of these patients (57.1%) initially presented with subarachnoid hemorrhage (SAH), one of which was secondary to a traumatic pseudoaneurysm. The mean length of time since initial treatment in the coil group was 28.1 months (range 1–84 months). Among those patients presenting with SAH, the mean length of time between initial and subsequent treatment was 7.0 months (range 1–17 months). Three patients were

TABLE 1. Patient characteristics and indications for treatment

Case No.	Age (yrs), Sex	Aneurysm Location	Initial Status	Prior Tx	Time From Initial Tx (mos)	Max Diameter (mm)	Indication for Re-Tx*
1	46, M	Lt OA	Ruptured	Coiling	17	4.2	Residual
2	55, M	Lt PCoA	Ruptured	Coiling	9	4.1	Residual
3	28, M	Rt paraclin ICA	Ruptured	Coiling	1	11.2	Recanalization
4	36, M	Lt paraclin ICA	Ruptured	Coiling	1	3.6	Residual
5	55, F	Lt paraclin ICA	Unruptured	Coiling	20	2.9	Recanalization
6	57, M	Lt OA	Unruptured	Coiling	65	5.9	Recanalization
7	48, F	Rt OA	Unruptured	Coiling	84	5.7	Recanalization
8	54, F	Lt OA	Ruptured	Clipping	204	13.2	Recanalization
9	56, F	Rt OA, rt PCoA	Unruptured	Clipping	74	6.4; 4.1	Recanalization
10	57, F	Lt AChA	Unruptured	Clipping	70	4.4	Recanalization
11	12, F	Rt MCA	Unruptured	Clipping	7	15.3	Residual
12	71, M	Lt cav ICA	Unruptured	FD	7	10.9	Residual
13	35, M	Rt petr ICA	Unruptured	FD	17	15.4	Residual

AChA = anterior choroidal artery; cav = cavernous; FD = flow diversion; OA = ophthalmic artery; paraclin = paraclinoid; PCoA = posterior communicating artery; petr = petrous; Tx = treatment.

* Aneurysms were classified as "recanalization" if at least 1 diagnostic angiogram demonstrated complete aneurysm occlusion prior to demonstration of recurrence.

treated for residual aneurysms that failed to completely occlude following prior treatment (Fig. 1). The other 4 patients experienced recanalization of an aneurysm that had demonstrated complete occlusion on prior angiography. Based on aneurysm location, endovascular treatment was preferred over microsurgical clipping, and given the prior failed treatment attempts, PED placement was undertaken to provide a scaffold for intimal overgrowth.

Four patients with 5 aneurysms had previously undergone microsurgical clipping, performed in the setting of SAH in 1 case. The mean time to treatment of aneurysm recurrence was 88.7 months (range 7–204 months). Four aneurysms were recurrent in nature, having angiographic documentation of prior complete occlusion. These were all initially treated at another institution, and given the significant amount of time since the initial surgery, endovascular means for further treatment was preferred. One patient was treated with microsurgical clipping of a giant middle cerebral artery (MCA) bifurcation aneurysm, and complete obliteration could not be achieved at that time (Fig. 2). The broad-necked remnant was most amenable to PED treatment, despite its MCA location.

Two patients with fusiform pseudoaneurysms had undergone prior treatment with PED, with a mean time since treatment of 12 months (range 7–17 months). One of these patients (Case 12) initially presented with a sixth cranial nerve palsy, while the other (Case 13, Fig. 3) initially presented with a dissecting pseudoaneurysm. Both patients demonstrated a substantial decrease in aneurysm size, although with a significant degree of residual, following the initial PED procedure. Residual aneurysm was predominantly located at the proximal and distal regions of prior treatment, and given the marked improvement following initial PED placement, additional PED placement was pursued.

The mean number of PEDs used was 1.3 (range 1–2) for saccular and blister aneurysms and 3 (range 1–5) for fusiform aneurysms.

Clinical and Angiographic Outcomes

There were no periprocedural complications in any group treated for recurrent aneurysms. Among the 7 patients previously treated with endovascular coiling, 1 patient was lost to follow-up. Of the 6 patients in this group who did have angiographic evaluation (Table 2), 5 under-

FIG. 1. Case 1. PED treatment for aneurysm residual following prior endovascular coiling. Left ICA digital subtraction angiography (lateral view). This patient initially presented with a ruptured left ophthalmic aneurysm (A), which was subsequently coiled (B), leaving a small neck remnant. Due to growth of the residual aneurysm (C), a PED was placed, resulting in complete occlusion at 6 months' follow-up (D).

FIG. 2. Case 11. PED treatment for aneurysm residual following prior microsurgical clipping. Right ICA digital subtraction angiography (anteroposterior [AP] view). This patient initially presented with an unruptured right giant MCA bifurcation aneurysm (A), which was subsequently clipped, leaving a small neck remnant (B). Due to growth of the residual aneurysm (C), a PED was placed, resulting in complete occlusion at 6 months' follow-up (D).

went angiography at 6 months after PED treatment, with complete occlusion seen in 4 (80%) of 5 cases, and 5 had radiographic follow-up at 12 months, with all 5 (100%) of these studies demonstrating complete occlusion. The single patient with Raymond 2 filling at 6 months did undergo repeat angiography at 12 months, and the repeat study demonstrated complete occlusion. No delayed complications were observed with a mean follow-up of 26.1 months

TABLE 2. Radiographic and clinical outcomes following PED treatment for recurrent previously treated aneurysms

Case No.	Angiogram Results		mRS Score	
	6 Mos	Latest FU (mos)	Pre-PED	Latest FU (mos)
1	Complete	Complete (16)	0	0 (36)
2	Partial	Complete (15)	0	0 (30)
3	Complete	Complete (21)	5	5 (21)
4	Complete	Complete (19)	5	2 (19)
5	NA	NA	0	NA
6	NA	Complete (13)	0	0 (13)
7	Complete	NA	0	0 (6)
8	Complete	Complete (31)	0	0 (31)
9	Complete	Complete (15)	0	0 (24)
10	Complete	Complete (37)	0	0 (37)
11	Complete	Complete (22)	0	0 (22)
12	Complete	NA	3	6 (8)
13	NA	Complete (13)	0	0 (13)

FU = follow-up; NA = not applicable.

Aneurysm occlusion is classified as either complete or partial. One patient (Case 5) was lost to follow-up.

(range 6–53 months). Four patients had a preprocedural and postprocedural mRS score of 0. Two patients presented with mRS score of 5, with one improving to an mRS score of 2 postprocedurally. The patient lost to follow-up presented with an mRS score of 0.

Regarding the 4 patients who had previously undergone microsurgical clipping, complete occlusion was seen in all 4 (100%) on 6- and 12-month follow-up angiography. There were no delayed complications, with a mean clinical follow-up of 27.7 months (range 21–33 months). All 4 patients had preprocedural and postprocedural mRS scores of 0.

Regarding the 2 patients treated with PED following failed prior PED treatment, 1 patient had complete occlusion of the ICA at 6 months' follow-up, although with no new clinical sequelae. The other patient experienced com-

FIG. 3. Case 13. PED treatment for aneurysm residual following prior PED treatment. Right ICA digital subtraction angiography (AP view). This patient presented following a fall with a dissecting pseudoaneurysm of the right petrous ICA (A), which was treated with 4 telescoping PEDs. Follow-up angiography revealed diminished size of the pseudoaneurysm, although with some residual, which was treated with 2 additional PEDs (B). Complete occlusion was seen at 13 months' follow-up (C).

plete aneurysm occlusion, with an mRS score of 0 and clinical follow-up of 17 months.

Discussion

The introduction of the PED revolutionized intracranial aneurysm management, particularly for large, wide-necked aneurysms of the ICA. The efficacy of this device, achieving a high aneurysm occlusion rate of 93%–94%, has made it a particularly appealing tool in endovascular neurosurgery.^{20,21,25} The significant recurrence rate in previously treated aneurysms has prompted an increased use of the PED in these aneurysms as a second-line treatment. Despite the overwhelming efficacy in untreated aneurysms, initial experience demonstrated decreased efficacy in previously treated aneurysms with a reported 68.7%²⁰ complete occlusion rate and prior treatment as a predictor of PED treatment failure.²² While prior treatment failure certainly places the patient at risk for further recurrence, the PED provides a distinct advantage in restoring physiological cerebral flow dynamics and providing a scaffold for endothelialization. In fact, numerous studies have demonstrated equivalent efficacy for the use of PEDs in treatment-naïve and recurrent aneurysms alike.

PED Following Failed Endovascular Coiling

Few studies have specifically evaluated the safety and efficacy of PED treatment following recurrence of previously coiled aneurysms. Nonetheless, placement of a PED as a secondary treatment following failure of endovascular coiling has a reported efficacy of 69%–93.3%,^{2,5,9,11,14,18,20,21} although many of these studies pooled initial treatments into a single cohort for evaluation. The only studies evaluating the outcome of PED placement in this specific subgroup of recurrent aneurysms in isolation (Table 3) revealed a complete obliteration of 76.7%⁹ and 69.2%.¹⁸ When combined with those demonstrating near-complete occlusion (> 90%), this increased to 86.7% and 100%, respectively, consistent with radiographic outcomes for PED placement in untreated aneurysms⁶ and with those seen in microsurgical clipping.²⁴ Similarly, among those patients treated with a PED following endovascular coiling at our institution, 80% demonstrated complete occlusion at 6 months, and 100% demonstrated complete occlusion at 1 year. No adverse clinical sequelae were observed, a result consistent with prior published reports in this subgroup. While both ischemic and hemorrhagic complications have been observed, the risk of significant neurological sequelae appears to be 3%–5.6%.^{2,9} Furthermore, our patients had no further recurrence or clinical symptomatology at a mean follow-up of 26.1 months, revealing that endovascular treatment with PED for recurrent previously coiled aneurysms is a safe, effective, and durable treatment option. For patients initially presenting with ruptured aneurysms, at which time PED placement carries substantial risk, treatment with a PED following failed endovascular coiling provides a scaffold for neointimal formation and vessel reconstruction, generating a more durable result.

PED Following Failed Stent-Assisted Coiling

Numerous studies have evaluated the safety and effi-

TABLE 3. Outcomes of PED treatment for recurrent previously treated aneurysms

Prior Tx & Authors	No. of Pts	Complete Occlusion	Clinical Outcome
Primary coiling			
Daou et al., 2015	33	76.7%	3% IPH (1)
Kühn et al., 2016	18	69.2%	No sequelae
Stent or stent-assisted coiling			
Fischer et al., 2012	30	65%	13%; CVA (2), IPH (2)
Daou et al., 2016	21	55.6%	14.3%; CVA (2), IPH (1)
Heiferman et al., 2016	25	38%	8%; TIA (1), IPH (1)
FD			
Becske et al., 2016	4	50%	Not reported
Microsurgical clipping			
Ding et al., 2014	2	50%	No sequelae
Adeeb et al., 2016	7	100%	No sequelae
Kalani et al., 2016	2	100%	No sequelae
Kühn et al., 2016	6	60.0%	No sequelae
Gross et al., 2017	8	100%	Fatal distal hemorrhage (1)

CVA = ischemic cerebrovascular accident; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; pts = patients; TIA = transient ischemic attack.

Studies directly evaluating the clinical and radiographic outcomes of patients secondarily treated with the PED following failed primary coiling, stent-assisted coiling, flow diversion, or microsurgical clipping. Values in parentheses are numbers of cases.

cacy of PED placement for aneurysm recurrence following previous treatment with either stenting alone or stent-assisted coiling.^{5,8,14,16,19–21} While this has been described in numerous reports, 3 published studies directly evaluated the safety and efficacy of PED in this subset of recurrent aneurysms (Table 3). In achieving complete aneurysm occlusion, reported efficacy ranged from 38% to 65%, a significantly lower rate than would be expected in PED use for treatment-naïve aneurysms.^{8,14,16} The incidence of significant adverse neurological sequelae tends to be substantially higher for previously stented aneurysms as well. Such sequelae, including transient ischemic attacks and major ischemic and hemorrhagic events, were observed in 8%–14.3% of cases. The presence of a stent in situ may hamper proper deployment and full wall apposition of the PED, decreasing its efficacy and increasing thrombogenicity. Due to this, certain techniques have been suggested, such as balloon angioplasty or distal placement of the intermediate catheter, which may improve delivery of the PED within a prior stent.^{5,19} Nonetheless, providers should be aware that utilization of a PED for recurrence following stent placement appears to be less effective than in untreated aneurysms and may carry a worse safety profile.

PED Following Failed Flow Diversion

Recurrent or residual aneurysms following PED placement can often be successfully treated with de-escalation

of the dual-antiplatelet regimen. When this fails to allow aneurysm occlusion, further treatment measures may need to be undertaken. Given that the PED is still in its infancy, little literature exists regarding PED failures and treatment options for recurrent aneurysms following prior PED apart from a few case reports.^{3,7,15} In a study evaluating the treatment of 119 unruptured aneurysms with a PED, 7 patients experienced occlusion failure, and in 3 of the 7 cases, this residual was treated with a second PED.⁷ Unfortunately, adequate follow-up to assess the durability of this second treatment was not available. When evaluating the 3-year follow-up results for the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial, the investigators found that 15 patients had a residual aneurysm or residual neck. Four of these patients underwent further treatment with a second PED (Table 3),³ and 2 (50%) of these 4 progressed to complete occlusion. The 2 patients treated with PEDs at our institution following failed flow diversion each presented with large fusiform aneurysms of the ICA, requiring multiple stents during their first and second treatments. Both patients primarily exhibited residual aneurysm at the proximal and distal portion of the treated segment, which largely guided the decision to place additional stents specifically at these sites. Given this significant amount of intraluminal metal, it is perhaps not surprising that 1 patient had complete vessel occlusion. Nonetheless, particularly in fusiform aneurysms, the reconstructive ability of PEDs makes them an attractive option.

PED Following Failed Microsurgical Clipping

Microsurgical clipping has long been regarded as the most efficacious and durable option for complete aneurysm occlusion. While the rate of aneurysm obliteration following clipping is 87%, retreatment rates hover around 4.5%.²⁴ and aneurysms that recur following microsurgical clipping carry substantial morbidity with a hemorrhage rate of nearly 50%.²³ A number of case reports and series have demonstrated efficacy in PED treatment of recurrent aneurysms following prior clipping with minimal complications.^{1,5,12,14,15,17,18,20} Among studies that have specifically evaluated outcomes following PED treatment in this recurrent subtype (Table 3), reported rates of complete aneurysm occlusion have ranged from 50% to 100%.^{1,12,15,17,18} One patient developed a fatal distal hemorrhage shortly after the procedure, although no other complications were observed.¹⁵ Similarly, our experience with the use of PEDs in these patients has been overwhelmingly positive, with a 100% rate of complete occlusion and no adverse complications. Given our mean duration of follow-up of 27.7 months for these patients, this treatment appears to be both durable and highly effective.

Limitations

This study has several limitations. First, the retrospective nature of the study introduces potential bias. Second, this study reveals outcomes from a single institution with significant experience in flow diversion techniques. Finally, the number of patients, particularly those treated with PED following failed prior flow diversion treatment, is quite limited. While interpretation of treatment results based on this small population must remain guarded, the

observed outcomes are similar to those reported for other published studies.

Conclusions

The introduction of the PED marked a significant paradigm shift in the endovascular treatment of intracranial aneurysms. PED treatment of a recurrent aneurysm following a prior failed stent appears to be less effective than PED use in untreated aneurysms while carrying a worse safety profile. The treatment of recurrent aneurysms following previous endovascular coiling, flow diversion, or microsurgical clipping is associated with a high rate of complete occlusion and minimal morbidity.

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Disclosures

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Author Contributions

Conception and design: Dornbos, Powers. Acquisition of data: Dornbos, Karras, Wenger, Youssef, Powers. Analysis and interpretation of data: Dornbos, Karras, Wenger. Drafting the article: Dornbos, Priddy. Critically revising the article: Dornbos, Karras, Wenger, Priddy, Nimjee, Powers. Reviewed submitted version of manuscript: Dornbos, Karras, Wenger, Priddy, Nimjee, Powers. Approved the final version of the manuscript on behalf of all authors: Dornbos. Administrative/technical/material support: Nimjee, Powers. Study supervision: Dornbos, Nimjee, Powers.

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