Off-label uses of the Pipeline embolization device: a review of the literature

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The Pipeline embolization device (PED) is the most widely used flow diverter in endovascular neurosurgery. In 2011, the device received FDA approval for the treatment of large and giant aneurysms in the internal carotid artery extending from the petrous to the superior hypophyseal segments. However, as popularity of the device grew and neurosurgeons gained more experience, its use has extended to several other indications. Some of these off-label uses include previously treated aneurysms, acutely ruptured aneurysms, small aneurysms, distal circulation aneurysms, posterior circulation aneurysms, fusiform aneurysms, dissecting aneurysms, pseudoaneurysms, and even carotid-cavernous fistulas. The authors present a literature review of the safety and efficacy of the PED in these off-label uses.

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IN recent years, the Pipeline embolization device (PED) has gained popularity as a treatment option for intracranial aneurysms. This flow diverter is an endoluminal, self-expanding, braided mesh tube made with 48 strands of platinum-tungsten and cobalt-chromium-nickel alloy wires.^{5,54} It works by diverting blood flow away from the aneurysm, leading to thrombosis of the aneurysm while also maintaining patency of the parent vessel.⁵⁴ The device has proven to be a safe and effective therapy for large, giant, and complex intracranial aneurysms.³⁸ In a comparative study of large unruptured saccular aneurysms, the PED provided higher aneurysm occlusion rates than coiling, with no additional morbidity and similar clinical outcomes.¹⁴ The authors of these studies concluded that the PED might be a preferred treatment option for this subtype of aneurysms.

As of 2011, the PED has gained FDA approval for use in adults with giant and large aneurysms that extend from the petrous to superior hypophyseal segments of the internal carotid artery (ICA).⁵⁴ Although initially developed for that use, over time its off-label uses have expanded to include a variety of aneurysm types including previously treated aneurysms, ruptured aneurysms, posterior circula-

tion aneurysms, small aneurysms, distal aneurysms, fusiform aneurysms, dissecting aneurysms, pseudoaneurysms, and carotid-cavernous fistulas (CCFs). This review article discusses some of those off-label uses and the results attained across institutions by using this device.

Methods

Articles eligible for our literature review were initially searched using PubMed with the term “Pipeline Embolization Device.” After we developed a list of off-label uses from our initial search, we expanded it to include individual diagnoses, using search terms including “ruptured aneurysms,” “small aneurysms,” “distal circulation,” “posterior circulation,” “previously stented aneurysms,” “previously coiled aneurysms,” “fusiform aneurysms,” “dissecting aneurysms,” “pseudoaneurysms,” and “carotid cavernous fistulas.” All articles within these searches were screened, and we included articles focusing on the use, safety, and efficacy of the PED for these specific off-label uses. These articles included large prospective and retrospective reviews, smaller case series, and case reports. Table 1 summarizes the studies that were conducted over

ABBREVIATIONS ACA = anterior cerebral artery; ACoA = anterior communicating artery; CCA = cavernous carotid aneurysm; CCF = carotid-cavernous fistula; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PED = Pipeline embolization device; PRU = P2Y12 reaction unit; SAH = subarachnoid hemorrhage.

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TABLE 1. Reported studies on the safety and efficacy of the PED for its off-label uses

Off-Label Use & Study	No. of Aneurysms	Complete Occlusion Rate (no.)*	Complication Rate (no.)†	Mortality Rate (no.)‡
Previously treated aneurysms				
Chalouhi et al., 2014 ¹³	15	64.3% (9/14)	6.7% (1)‡; 26.7% (4)§	0% (0)
Daou et al., 2015	32	76.7% (23/30)	3% (1)‡	0% (0)
Daou et al., 2016 ²³	21	55.6%	14.3% (3)	NA
Kühn et al., 2016 ⁴¹	24	66.7% (10/15)	0% (0)	0% (0)
Ruptured aneurysms				
Lin et al., 2015 ⁴⁵	26	78.3% (18/23)	19.2% (5)¶	11.5% (3)
Cruz et al., 2013	20	94% (15/16)	15% (3)	5% (1)
McAuliffe et al., 2012 ⁵⁰	11	88.9% (8/9)	0% (0)	18.2% (2)
Chalouhi et al., 2015 ¹⁵	20	80% (12/15)	5% (1)¶	5% (1)
Chan et al., 2014	8	100% (8/8)	25% (2)	0% (0)
Small aneurysms				
Chalouhi et al., 2015 ¹⁶	100	72% (54/75)	3% (3)	0% (0)
Chalouhi et al., 2014 ¹¹	40	80% (31/39)	5% (2)	0% (0)
Saatci et al., 2012	155 of 251	93.8% (136/145)	1% (2)‡; 13.1% (25)§**	0.5% (1)**
Griessenauer et al., 2017	149	87% (107/123)	Neurological 15.4% (23); thromboembolic 8.7% (13); procedural 6% (9)	0% (0)
Lin et al., 2013	44	66.7% (14/21)	2.3% (1)‡¶; 6.8% (3)§	2.3% (1)
Distal circulation aneurysms				
Lin et al., 2016	28	77.8% (21/27)	Periprocedural 10.7% (3); postprocedural 21.4% (6)	0% (0)
Nossek et al., 2017	5	100% (5/5)	0% (0)	0% (0)
Zanaty et al., 2014	10	77.8% (7/9)	30% (3)	0% (0)
Puri et al., 2016	7	100% (6/6)	0% (0)	0% (0)
Martínez-Galdámez et al., 2015	25	64% (14/22)	4% (1)‡; 8% (2)§; intraprocedural 12% (3)	0% (0)
Dabus et al., 2017	20	69% (11/16)	5% (1)‡¶; 5% (1)§	5% (1)
Clarençon et al., 2017	8	71.4% (5/7)	0% (0)	0% (0)
Posterior circulation aneurysms				
Phillips et al., 2012	32	96% (22/23)	Permanent neurological 9.4% (3); infarction 9.4% (3); hematoma 6.3% (2)	0% (0)
Munich et al., 2014	12	90% (9/10)	25% (3)¶	8.3% (1)
Chalouhi et al., 2013 ¹²	7	50% (3/6)	0% (0)	0% (0)
Albuquerque et al., 2015	17	78.6% (11/14)	5.9% (1)‡; 23.5% (4)	0% (0)
Zumofen et al., 2015	6	100% (6/6)	0% (0)	0% (0)
Fusiform & dissecting aneurysms				
Fischer et al., 2014	69	67% (33/49)	Clinical impairment 12% (8); morbidity 5%	8%
Monteith et al., 2014	24	31.8% (7/22)	16.7% (4)‡; 4.2% (1)§	4.2% (1)
de Barros Faria et al., 2011	23	69.5% (16/23)	8.7% (2)	0% (0)
Brzezicki et al., 2016	13	75% (6/8)	7.6% (1)	0% (0)
Pseudoaneurysms				
Tsang et al., 2015	7	100% (5/5)	Periprocedural infarction 14.3% (1); delayed thrombosis 42.9% (3)	0% (0)
Mostly case reports				
CCF				
Mostly case reports				

NA = not available.

* Complete (100%) occlusion rate at the latest follow-up.

† These refer to procedure-related complications and death.

‡ Major procedure-related complication that led to significant morbidity.

§ Minor procedure-related complication that led to no or minor morbidity.

¶ Includes deaths in the complication rate.

** Rates from a larger set of aneurysms, because the off-label use comprised only a subset of aneurysms.

the years to assess the safety and efficacy of the PED in its off-label uses.

Previously Treated Aneurysms

Conventional therapies for intracranial aneurysms are microsurgical clipping and endovascular coiling.⁴⁷ Two well-conducted, randomized, controlled trials have evaluated these 2 methods in the treatment of intracranial aneurysms and looked at recurrence and retreatment rates.^{7,66} In the International Subarachnoid Hemorrhage Trial (ISAT), 9.0% of patients treated with coiling and 0.85% of patients treated with microsurgical clipping had to be retreated due to recurrence.⁷ In the Barrow Ruptured Aneurysm Trial (BRAT), the retreatment rates at the 3-year follow-up were 13% and 5% for coil-treated and clip-treated patients, respectively.⁶⁶ Similar recurrence and retreatment rates were described in later studies as well.^{8,10,28} Given the not insignificant rate of recurrence associated with conventional treatments (coiling in particular), several investigators have studied the safety and efficacy of the PED as a treatment for recurrent aneurysms after previous coiling, stenting, or microsurgical clipping.

Chalouhi and colleagues presented one of the earlier studies that looked at the PED as treatment for recurrent aneurysms.⁸ Their series included 15 patients with recurrent aneurysms; 8 previously treated with coiling, 4 with stent insertion and coiling, 2 with telescoping stent, and 1 with surgical clipping. Of the patients available for follow-up, 64.3% had complete occlusion and 28.6% had near-complete occlusion. One patient (6.7%) had a major complication and 4 (26.7%) had minor complications. The authors believed that the morbidity rates associated with PED might be higher than those of more traditional methods. This same group later looked at subsets of patients with recurrent aneurysms that were previously coiled and previously stented.^{23,24} One study followed 32 patients with single lesions who had recurrence of previously coiled aneurysms, and investigators found a total rate of complete and near-complete occlusion of 86.7%, a complication rate of 3%, and no mortalities.²⁴ In a series of 21 previously stented aneurysms, the complete occlusion rate after PED placement was found to be 55.6% and the complication rate was 14.3%.²³ In this second study, the authors compared these results with a group of patients who underwent PED placement for aneurysms not previously stented. They concluded that the PED was less effective in managing previously stented aneurysms compared with nonstented aneurysms, and can also be associated with a higher complication rate in the previously treated aneurysms.

Kühn et al. found promising results in their series of 24 patients who underwent PED placement for previously clipped and coiled aneurysms.⁴¹ The complete or near complete occlusion rates of previously treated ruptured and unruptured aneurysms was 94.4% at 6 months and 93.3% at 12 months. These investigators also did not observe any severe procedure-related complications. A report of 2 patients with recurrent previously clipped aneurysms who underwent PED placement also presented good outcomes.²⁸ This was one of the few reports that looked specifically at recurrent aneurysms that had previ-

ously undergone microsurgical clipping. There is a need for larger studies to assess the safety and efficacy of the PED in treating such cases.

Ruptured Aneurysms

The PED has mostly been used to treat unruptured aneurysms, whereas its use for acutely ruptured aneurysms has been limited and is theoretically contraindicated, given the need for dual antiplatelet therapy. When treating aneurysmal subarachnoid hemorrhages (SAHs), multiple additional intracranial procedures may be required, such as external ventricular drain placement, ventriculoperitoneal shunt insertion, or decompressive craniotomy for hematoma evacuation.⁴⁵ These subsequent surgeries can be complicated by the dual antiplatelet therapy that is required in conjunction with PED placement. In addition, placement of flow diverters like the PED results in gradual rather than immediate thrombosis of the aneurysm. Considering this and the antiplatelet therapy, the risk of rehemorrhage would be theoretically higher with the PED.⁴⁵ However, in certain cases of complex ruptured aneurysms, the PED may still serve as a good alternative (and sometimes may be the only available option) because these aneurysms are anatomically and technically more difficult to treat using standard techniques.⁴⁵

A number of case series have assessed the outcomes of the PED for acutely ruptured aneurysms. Lin and colleagues presented the largest series on PED treatment for ruptured aneurysms, looking at a total of 26 cases.⁴⁵ The periprocedural complication rate was 19.2% (5/26) and included 3 deaths. Complete occlusion was achieved in 78.3%, and a modified Rankin Scale (mRS) score of 0–2 was reported in 76.9%. The authors of this study concluded that due to the high complication rate, this procedure should only be used for ruptured aneurysms that are too difficult to treat by other, more traditional means. Similar results were seen in other studies as well. A series of 20 patients with aneurysmal SAHs who underwent PED placement had a procedure-related complication rate of 15% and 1 procedure-related death.²⁰ Aneurysm occlusion rates were 75% at the 6-month follow-up and 94% at the 12-month follow-up. A smaller series of 11 cases was presented by McAuliffe et al.⁵⁰ There were 2 deaths due to acute aneurysm rerupture and, of the remaining 9 patients, 8 had complete occlusion at the 6-month follow-up. There were no reported procedure-related symptomatic complications.

Chalouhi et al. presented a series of 20 patients undergoing PED placement for acutely ruptured aneurysms.¹⁵ A procedure-related complication was seen in only 1 patient, who experienced an acute aneurysm rerupture, leading to her death. The occlusion rate was 80%, and 95% of patients had a favorable outcome (mRS score of 0–2) at most recent follow-up. Last, a small series of 8 ruptured dissecting aneurysms had 2 procedure-related symptomatic complications and complete obliteration of all 8 aneurysms at follow-up.¹⁷

Furthermore, certain anticoagulation protocols can be put into place to prevent the feared consequences associated with PED placement in ruptured aneurysms due to dual antiplatelet therapy. The standard management for

the prevention of thromboembolic events when using flow diverters is pretreatment with aspirin and clopidogrel for 7–10 days prior to the procedure.⁹ When treating ruptured aneurysms with the PED in conjunction with this dual antiplatelet therapy, there is a concern for hemorrhagic complications. Chalouhi and colleagues described a new regimen for anticoagulation that was recently implemented in the hope of minimizing the risk of thromboembolic and hemorrhagic complications.⁹ The protocol entails starting a maintenance infusion of tirofiban, a glycoprotein IIb/IIIa inhibitor, immediately after the PED is placed and discontinuing after 2 hours, and also administering a single dose of aspirin and clopidogrel intraoperatively with no pretreatment prior to the procedure. They assessed the safety and efficacy of this protocol in 46 patients being treated with the PED for aneurysms, and complications were found in 2 patients (4.3%). Of the 2 complications, only 1 was hemorrhagic and did not lead to a permanent morbidity. From this experience it was concluded that such a protocol is safe and is a good alternative to the standard dual antiplatelet regimen, especially in patients being treated for ruptured aneurysms.

In sum, the PED may be particularly helpful in acutely ruptured aneurysms that are not amenable to coiling or clipping. It can also be used in a staged fashion 1 or 2 weeks after partial coiling of the aneurysm dome. It is generally preferable to place an external ventricular drain if treatment with the PED is contemplated.

Small Aneurysms

Although FDA approval for the PED is for giant and large aneurysms, many institutions have expanded the use of this device to include small aneurysms as well. The cut-off margin of what defines a small aneurysm differs among physicians, but was reported to be < 7–10 mm.^{11,16,35,44,64} Many studies have found favorable outcomes, suggesting that PED is a safe and efficacious treatment option for small aneurysms, similar to the results of PED use for large and giant aneurysms.¹⁶

Chalouhi and colleagues used the PED in the treatment of 100 patients with small aneurysms (≤ 7 mm).¹⁶ In their series, 85% of aneurysms were adequately (completely or nearly completely) occluded at the most recent follow-up, and the rate of procedure-related, symptomatic complications was as low as 3%. They concluded that the PED was associated with low complication rates and high occlusion rates when used for the treatment of small aneurysms. In another study conducted by the same group, the results of the PED for 40 small aneurysms that were matched and compared with 160 small aneurysms treated with stent-assisted coiling were reported.¹¹ The complication rate was 5% in the PED cohort and 3% in the stent-coil group. The PED group had a higher aneurysm occlusion rate (80%) compared with the stent-coil group (70%), but this did not reach statistical significance. The authors concluded that the 2 procedures had similar complication rates and clinical outcomes, making the PED a promising alternative option to consider.

In one of the larger series, 155 small aneurysms (of a total of 251) were treated with the PED.⁶⁴ In this study by Saatci et al., 93.8% of small aneurysms had total occlu-

sion within 6 months of the procedure, and the overall permanent morbidity and mortality rates were 1% and 0.5%, respectively. Griessenauer et al. presented their results in 149 small (≤ 7 mm) aneurysms, making theirs the largest series assessing the use of PED for small aneurysms specifically.³⁵ The complete occlusion rate was 87% at most recent follow-up. The rate of thromboembolic and symptomatic procedural complications was 8.7% and 6%, respectively, and there was a single death (0.9%) that was not related to the PED placement. In another study looking at 44 small aneurysm cases, Lin et al. found adequate (complete or nearly complete) occlusion in 80% of small aneurysms within 6 months of treatments.⁴⁴ One patient (2.3%) experienced a major complication of early SAH that led to the death of that patient. Three patients (6.8%) also experienced periprocedural complications, all of which were successfully managed and resolved without any additional complications. This study reported lower complication rates and a higher rate of early angiographic success when using the PED to treat small aneurysms compared with large and giant aneurysms. The favorable outcomes of all the studies presented here suggest that the PED is a safe and efficient therapy that should be considered for the treatment of small aneurysms. In our institution, the PED has become a first-line option for small and simple intracranial aneurysms.

Distal Circulation Aneurysms

Distal aneurysms arise from the middle cerebral artery (MCA) and anterior cerebral artery (ACA) distal to the anterior communicating artery (ACoA) complex.^{46,59} They account for 5%–10% of all intracranial aneurysms.⁵⁹

There are theoretical contraindications to using PED for distal circulation aneurysms. The parent arteries of such aneurysms are small (< 2.5 mm in caliber), which makes PED placement technically more challenging.⁵⁴ Complications related to PED placement in such small vessels include stenosis and parent artery occlusion secondary to neointimal hyperplasia, or an inflammatory response.³⁰ However, because the process of hyperplasia and inflammation would be gradual, in-stent stenosis would also be expected to be gradual, allowing time for collateral vasculature formation. Distal aneurysms often arise at branch points, and so there is a risk of occluding a major branch. In addition, the A₁ segment of the ACA and the M₁ segment of the MCA, where many distal aneurysms arise, have a lot of lenticulostriate perforating vessels that can also be covered and occluded by PED placement, leading to strokes and secondary neurological deficits.^{46,54} In addition to the small caliber of the vessels associated with these aneurysms, there is also a more tortuous vasculature with more branches in the distal circulation, which poses another technical challenge. However, the more recent PEDs have been designed to be smaller and shorter, allowing for easier navigation and deployment of the device.³⁰

For all of these above-mentioned factors, use of the PED for distal circulation aneurysms has been met with some reluctance in the neurosurgical field. However, it is being considered more often as an alternative, especially in cases of distal aneurysms that are deemed challenging to treat with the traditional treatment options. Further-

more, the gold standard treatment for distal aneurysms, microsurgical clipping, although associated with high occlusion rates, also has an increased mortality and morbidity rate.^{59,69} Balloon- and stent-assisted coil embolization may require placement of multiple catheters into the parent vessel and therefore, when used in small parent vessels, may have an increased risk of thromboembolic complications.⁶² In such instances, a safer alternative in complicated cases can be of significant value.

A number of case reports and retrospective studies have assessed the safety and efficacy of PED use for distal circulation aneurysms. Lin et al. presented a retrospective review of 28 patients with distal aneurysms treated with PED.⁴⁶ At an average follow-up of 7.7 months, 77.8% of patients were found to have complete aneurysm occlusion. The complication rate during the periprocedural period (< 30 days) was 10.7%, with no deaths. The majority of patients (96.4%) had a good outcome, with mRS scores between 0 and 2, and 1 patient had a fair outcome, with an mRS score of 3. In a smaller series of 5 distal aneurysms presented by Nossek et al., all patients had complete occlusion between 5 and 14 months of device placement.⁵⁹ In this series the mean follow-up period was 21.25 months, and during that time none of the patients developed parent vessel occlusion or in-stent stenosis. Branch vessel patency was maintained in 4 of the 5 patients, with the fifth patient showing asymptomatic occlusion of the branch vessel with no clinical neurological deficits. Zanaty and colleagues reviewed 10 cases of MCA aneurysms treated with the PED.⁷¹ There was 1 periprocedural complication that improved after treatment, no deaths, and no technical complications in this series. The overall complication rate was 30% in this series, including periprocedural and long-term complications. Of the patients available for angiographic follow-up, 77.8% had complete occlusion of the aneurysm.

Puri and colleagues presented their experience treating 7 aneurysms distal to the circle of Willis.⁶² The complication rate was 0%, and of the 6 patients who were available for angiographic follow-up, there was complete aneurysm occlusion in all patients. Martínez-Galdámez et al. also looked at the use of PED to treat 25 aneurysms beyond the circle of Willis.⁴⁹ Their series had a complete occlusion rate of 64%, and the remaining 36% had significantly reduced residual filling. When evaluating side branches that were covered by PED placement, 79% were found to be patent at follow-up. Six patients (27%) had in-stent stenosis; however only 1 patient was symptomatic. There were 2 minor postoperative events that both resolved spontaneously within 24 hours, 1 major postoperative event, and no deaths, as well as 3 procedural complications that resolved without major deficits. In another series of 20 patients treated for complex ACA aneurysms with PED, the overall complete and near complete occlusion rates were 69% and 75%, respectively.²¹ One patient experienced a major complication of a large intraparenchymal hemorrhage, which led to his death, and 1 patient had a small caudate infarct with complete recovery. Similar to the above-mentioned occlusion rates, Clarençon et al. demonstrated a 71.4% complete occlusion rate in their series of distal ACA aneurysms treated with PED.¹⁹ There were no acute or delayed complications in this series.

Last, a few case reports also showed promising results. In 1 case, a fusiform aneurysm at the junction of M₃ and M₄ treated with PED resulted in complete aneurysm occlusion at the 3-month follow-up, a patent parent vessel, and no deficits in neurological function.³⁰ Furthermore, PED was also used in a pediatric case of distal ACA aneurysm. Angiographic follow-up showed complete occlusion of the aneurysm and the patient had no postoperative neurological deficits.⁶⁸ The promising outcomes of these studies support the use of the PED for treatment of aneurysms in the distal cerebrovascular circulation, especially in cases that are considered too difficult to treat using conventional methods.

Posterior Circulation Aneurysms

Numerous studies have demonstrated the safety and efficacy of the PED in the anterior circulation.^{18,48,51,56,64} However, the use of the PED in the posterior circulation is not as extensive due to the unique characteristics of the cerebral vasculature and aneurysms arising in this location. Specifically, numerous unforgiving perforator vessels arise in this area and supply brainstem structures; the occlusion of these perforators can lead to significant disabilities.^{53,60} Earlier studies looking into the use of the PED in the posterior circulation have demonstrated higher mortality and morbidity rates.^{60,65} Phillips and colleagues assessed the safety of PED placement in 32 patients with posterior circulation aneurysms.⁶⁰ The aneurysm occlusion rate was 85% of patients with > 6 months of follow-up and 96% of patients who were followed for > 1 year. Of the 21 patients who had basilar artery aneurysms, perforator infarctions were seen in 3 patients (14%), although just a single PED was used in each case. Phillips et al. concluded that clinical perforator infarction rates may be higher when the PED is placed within the basilar artery compared with the ICA.

More recent studies have demonstrated good outcomes with the device. Munich et al. assessed the outcomes in 12 patients with vertebrobasilar fusiform aneurysms treated with the PED.⁵³ The complete aneurysm occlusion rate was 90% in this study. Complications related to the procedure occurred in 3 patients, resulting in death in 1 of the cases and significant resolution in the other 2 cases. There were no thromboembolic complications seen in this series. The authors emphasized their strict adherence to adequate platelet inhibition to avoid such complications and also vigilant monitoring of patients receiving antiplatelet therapy to avoid hemorrhagic complications, and they were quite successful in their management. The need for long-term dual antiplatelet therapy in such cases was further supported by case reports that found delayed thrombosis after PED placement for large fusiform posterior circulation aneurysms in the cases in which antiplatelet therapy was altered or discontinued.^{32,40}

Chalouhi and colleagues presented their series of 7 patients with posterior circulation aneurysms.¹² They reported no procedural complications, perforating vessel infarcts, or new neurological deficits within the treated patients. Six patients were available for angiographic follow-up and of them, 3 had 100% occlusion, 2 showed significant decrease in aneurysm size, and 1 experienced

no change. In addition, the patency of perforator vessels was maintained in all cases. Another study treated 17 patients with posterior circulation aneurysms using the PED.¹ The authors found complete or near-complete aneurysm occlusion in all the patients available for follow-up. A procedure-related complication leading to permanent disability was seen in only 1 patient. A study by Zumofen and colleagues assessed the safety and efficacy of PED in the treatment of 6 nonsaccular P₁ or P₂ segment aneurysms.⁷² All patients had aneurysm occlusion within 1 year, the majority within 6 months. There were no new permanent neurological symptoms or aneurysm recurrences noted in this series.

Fusiform and Dissecting Aneurysms

Fusiform aneurysms can occur in the setting of atherosclerotic disease and progress slowly over time, with involvement of the entire circumferential vessel wall.³³ Dissecting aneurysms, on the other hand, often are a result of trauma or can occur spontaneously, and are caused by injury to and disruption of the internal elastic lamina. Due to their morphology, these types of aneurysms are considered challenging to treat using the standard surgical and endovascular methods. The PED may be a promising alternative for these otherwise challenging lesions that avoids parent vessel occlusion while sufficiently excluding the aneurysm.

Fischer et al. conducted one of the larger series, looking at 69 fusiform and dissecting aneurysms in 65 patients.³³ At the latest follow-up, complete occlusion was seen in 67% of patients and reduced perfusion in 29%. The morbidity rate was 5% and the mortality rate was 8%. Monteith and colleagues reviewed 24 cases of fusiform aneurysms treated with the PED.⁵² They found the procedure-related minor morbidity and mortality rates to be 4.2% and 4.2%, respectively, and found major complications in 16.7% of their patients. At their latest follow-up, 59% of patients had $\geq 95\%$ aneurysm occlusion. In their experience, the authors found the PED to be a safe and effective treatment for fusiform aneurysms with reasonable morbidity and mortality rates considering the complexity of these lesions.

A study conducted by de Barros Faria et al. followed 23 patients with dissecting aneurysms treated with the PED.²⁵ Of the 16 patients who were available for at least 3 months of follow-up, 87.5% had complete occlusion. The overall occlusion rate of all patients, regardless of follow-up time, was 69.5%. There were 2 procedure-related complications, both of which had complete resolution. In another study, 13 dissections presented in 11 patients, and of the 13 dissections, 11 were associated with pseudoaneurysms (discussed in further detail in the next section, *Pseudoaneurysms*).⁶ There was 1 nonsignificant procedure-related complication, and the complete occlusion rate at most recent follow-up was 75%. Other small series and case reports also presented favorable outcomes when using PED therapy for the treatment of dissecting aneurysms.^{34,42,70}

Pseudoaneurysms

Intracranial pseudoaneurysms can result from blunt or penetrating trauma, arterial dissection (as discussed in the previous section, *Fusiform and Dissecting Aneurysms*),

infection, radiation, or following surgery.^{2,3,37,67} Because they are not true aneurysms and are instead secondary to injury to the vessel wall, pseudoaneurysms lack a true, full-thickness wall and are contained only by a connective tissue layer.³ For this reason, they have an elevated risk of rupture, especially intraoperatively. However, endovascular interventions now allow for a less invasive means to treat these lesions. Traditionally, the treatment strategy has been parent artery sacrifice with or without revascularization, by open surgery or by endovascular means.² Flow diverters such as the PED allow for exclusion of the pseudoaneurysm while still maintaining parent vessel patency.

One of the first cases using the PED for a traumatic intracranial pseudoaneurysm was presented by Amenta et al.³ Their patient developed a pseudoaneurysm following surgery that was treated with the PED. Within 4 months, there was complete obliteration of the pseudoaneurysm and successful endoluminal reconstruction of the damaged vessel. A few other case reports and small series also demonstrated successful use of the PED to treat pseudoaneurysms.^{2,29,39,57}

The use of the PED is limited to pseudoaneurysms in which there is no active bleeding, because the efficacy of flow diverters depends on the lack of a significant pressure gradient across the pseudoaneurysm wall to promote thrombosis.² Kadkhodayan and colleagues present a case further emphasizing this.³⁷ Their patient initially presented with an actively bleeding pseudoaneurysm. The bleeding ceased spontaneously and a PED was placed shortly thereafter. However, just days later the patient presented again with rebleeding, and the vessel had to be sacrificed. The authors concluded that transient cessation of the bleeding is not sufficient to place PED for treatment. Use of the PED in cases of actively bleeding pseudoaneurysms would not be useful. Ischemic complications may also be associated with PED use. In a small series of 7 patients treated for postirradiated carotid pseudoaneurysms with the PED, 1 patient experienced multiple, periprocedural ischemic cerebral infarctions, and another 3 patients had delayed ICA thrombosis leading to a lacunar infarct in 1, whereas the other 2 remained asymptomatic.⁶⁷ Although the PED was effective in excluding the pseudoaneurysms, the authors concluded that the high risk of ischemic complications did not support the use of flow diverters as a first-line treatment option.

The limited number of studies assessing the safety and efficacy of the PED for pseudoaneurysm treatment present mixed results. Although a few case reports and small series have shown promising results, much larger and more extensive studies would be needed to establish the role of the PED in treating pseudoaneurysms. Frequently, the PED is the only alternative to vessel sacrifice for pseudoaneurysms. We currently use the PED as a first-line option for pseudoaneurysms unless there is evidence of active bleeding, in which case parent vessel occlusion is used.

Carotid-Cavernous Fistulas

A CCF is an abnormal connection between the carotid artery and cavernous sinus that causes shunted blood to flow from the carotid artery into the cavernous sinus, either directly (arising directly from the carotid artery) or

indirectly (arising from branches of the carotid artery).³¹ These lesions can occur spontaneously or as a result of trauma. Although the exact mechanism of formation is not known, there are many theories to explain the pathophysiology. The initial insult is injury to the vessels, which can be a direct tear from a bone fracture or the shear forces from trauma, rupture of a cavernous carotid aneurysm (CCA), or smaller breaks from chronic diseases such as arterial hypertension or atherosclerosis.³¹ The goal of treatment would be to occlude the CCF and restore normal flow through the ICA.

Unfortunately, only a handful of case reports demonstrate the use of the PED in treating CCFs. The earliest case was presented by Nadarajah et al., in which a young patient developed a posttraumatic, high-flow CCF that was then treated with the PED.⁵⁵ Follow-up angiograms confirmed successful treatment by showing no evidence of arteriovenous shunting. Pradeep et al. presented 2 additional cases of posttraumatic CCFs that were both adequately treated with the PED, leading to CCF occlusion and clinical improvement in both patients.⁶¹ Favorable outcomes using the PED were also seen in a case of a direct high-flow CCF that resulted from the rupture of a CCA.⁵⁸ A unique case was presented by Amuluru et al. Their patient had an unruptured CCA that was treated with PED placement.⁴ Postoperative angiograms revealed the formation of a direct CCF, which the physicians decided to treat with flow diversion, and the patient underwent a second PED procedure for the CCF. At the 12-month follow-up, angiograms showed complete resolution of the CCF and clinical improvement in the patient.

In the previously mentioned case report, CCF is presented as both a complication of PED placement in treatment of a CCA and also an off-label indication for the use of PED therapy.⁴ The CCF is a known complication of PED. In fact, a study by Roy et al. found a CCF rate of 11.4% in their series of 44 patients who underwent the PED procedure for CCA.⁶³ Lin et al. presented 2 such cases of direct CCFs that formed as a result of delayed aneurysm rupture following PED treatment of CCA.⁴³

In cases of posttraumatic and spontaneous CCF, the PED may be a possible treatment option; however, there is a lack of larger studies to confirm the results of the few reported case reports and small series presented here. It should be mentioned that traditional methods such as transvenous and transarterial embolization have an excellent safety-efficacy profile and should continue to be offered as a first-line therapy for these patients.

Potential Ways to Improve the Safety and Efficacy of PED Therapy

When assessing the safety of the PED, some major complications to consider are hemorrhagic and thromboembolic events. At our institution, we have thoroughly explored the occurrence of these complications and taken measures to improve the overall safety and efficacy of this procedure. The monitoring of P2Y₁₂ receptor inhibition, in P2Y₁₂ reaction units (PRUs), has been used to predict the incidence of hemorrhagic and thromboembolic complications, with the ideal preoperative range reported to be 60–240 PRUs.^{26,27} We reviewed 248 aneurysms in 231

patients treated with the PED at our institution to assess their PRU values and incidence of complications.²² Our results led us to believe that an optimal PRU range would be 70–150, because values < 70 were more likely to be associated with hemorrhagic complications and values > 150 had greater chances of thromboembolic complications. Although these cutoff values had a high sensitivity (80%), they had a low specificity (35%). Therefore, treating neurosurgeons should be aware that patients with preoperative PRUs outside this range can still undergo the procedure without developing hemorrhagic or thromboembolic complications, and assess their candidacy on a case-by-case basis. Nonetheless, PRU is a vital factor to consider in the decision-making process.

Another factor to assess that can affect the safety and efficacy of the PED procedure is the number of PEDs deployed. Chalouhi et al. presented the first study comparing complication rates, aneurysm occlusion rates, and postoperative outcomes in 178 patients undergoing treatment for aneurysms using a single PED (126 patients) versus multiple PEDs (52 patients).¹³ They found that although both groups have similar aneurysm occlusion rates at their latest follow-ups, the patients in whom a single PED was placed had a significantly lower complication rate and better overall clinical outcomes. Based on these results, using a single PED may be sufficient in adequately treating the aneurysm, while maintaining a low incidence of complications. In fact, at our institution, almost all aneurysms are now treated with a single PED.³⁶

Last, as physicians gain more experience with the PED procedure, the safety and efficacy is expected to increase as well. We previously presented the learning curve at our institution.³⁶ We assessed 120 aneurysms in 109 patients treated with the PED for intracranial aneurysms, divided into 3 consecutive, equal groups. The average procedure time significantly decreased from Group 1 to Group 3. The number of PEDs used also significantly decreased over time. The complication rates seen in the 3 groups (16.2%, 8.3%, and 5.6%, respectively) followed a downward trend, with a dramatic and significant decrease in the rate of major complications; from 10.8% in the first group to 0% in Groups 2 and 3. Results supported presence of a definite learning curve, proving that physician experience performing the procedure is a significant factor determining the overall safety of the technique. Extensive formal training on the PED procedure may be implemented for neurosurgeons to further enhance the safety and efficacy profile of this technique.³⁶

Conclusions

The PED has been studied and used extensively for its FDA-approved indications of large and giant aneurysms of the ICA. In the last few years, it has gained popularity in a number of off-label neurovascular uses. It has proven to be a safe and efficacious treatment option for many of these off-label uses, whereas others may still require larger, more extensive studies to draw conclusions. Nevertheless, the PED is a promising treatment alternative and should be considered by neurosurgeons for the treatment of complex neurovascular pathologies that may be deemed difficult

to treat by using conventional surgical and endovascular techniques.

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Disclosures

Drs. Jabbour and Tjoumakaris are consultants for Medtronic.

Author Contributions

Conception and design: Jabbour, Patel, Chalouhi, Atallah. Acquisition of data: Patel, Chalouhi, Atallah. Analysis and interpretation of data: Patel, Chalouhi, Atallah. Drafting the article: Patel, Chalouhi. Critically revising the article: Jabbour, Patel, Chalouhi. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Jabbour. Study supervision: Jabbour.

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