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J.L. Brisman

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What's Coming Down the Pipe—And Should We Be Excited, Concerned, or Both?

In the article entitled "Canadian Experience with the Pipeline Embolization Device for Repair of Unruptured Intracranial Aneurysms" in the current issue of *AJNR*, O'Kelly et al[1] report on the combined experience of 7 Canadian centers between July 2008 and December 2010 using the Pipeline Embolization Device (PED; Covidien, Irvine, California), a flow-diverting stent, to treat unruptured intracranial aneurysms. During this period, the combined teams treated 97 unruptured aneurysms and followed the patients radiographically and clinically. This article retrospectively reviewed the collected data. Technique and follow-up were heterogeneous among the centers and not controlled for. Mean aneurysm size was 19 mm, and mean aneurysm neck width was 8 mm. Stents were successfully deployed in 94/97 lesions, and occlusion or near-occlusion of the aneurysm was noted in 84.2% at a mean of 1.25 years of follow-up and 90% at 1 year of follow-up. At follow-up, 89.3% of patients were clinically stable or improved. There were 4 (4.3%) patients with a new neurologic deficit and 6 deaths (6.4% mortality) in the series. There were 7 postoperative intracranial hemorrhages, 3 thought to be from the treated aneurysm and 4 distal and ipsilateral to the treated parent vessel. In the cavernous aneurysm cohort ($n = 28$), all lesions were noted to be completely or nearly completely occluded at follow-up and there were no serious neurologic complications, hemorrhages, or deaths associated with Pipeline stent placement in lesions in this location. The authors concluded that the Pipeline may represent an important part of the evolving endovascular technology but is associated, particularly for noncavernous lesions, with significant potential complications that must be considered.

The PED is a low-porosity endovascular stent designed to treat intracranial aneurysms by acting as a flow diverter. In other words, the stent attempts to reconstruct the parent vessel harboring aneurysms, diverting blood flow away from the aneurysm itself, resulting in intra-aneurysmal thrombosis, endoluminal scaffolding, and restoration of normal flow in the parent vessel. Further intended results include a remodeled vessel with the development of neointimal proliferation, which may lead to increased aneurysm obliteration and decreased recurrence. The device, which was granted FDA approval in 2011 and boasts 3–5 times increased surface coverage compared with other intracranial stents on the market, was designed for the treatment of wide-neck large and giant saccular and fusiform aneurysms. Currently, FDA approval for use in the United States is strictly limited to the following criteria: age, >22 years; aneurysm neck, >4 mm; aneurysm size, >10 mm; and aneurysm location between the petrous and superior hypophyseal segments of the internal carotid artery. Absolute contraindications include patients with active bacterial infection, patients in whom dual antiplatelet therapy is contraindicated, patients who have not received dual antiplatelet agents before the procedure, and patients harboring a prior stent at the target aneurysm site.

The delivery requires a 6F sheath and a guide catheter system. The stent itself is deployed via a 0.027-inch microcatheter. The company recommends using a 0.014- or 0.016-inch wire. Stent deployment is accomplished via a slow unsheathing in conjunction with a push/pull and twisting motion that allows the stent to remodel the vessel as it is deployed. The deployment process is much slower than that with other intracranial stents, and resheathing is not possible. Premedication with dual antiplatelets and intraprocedural heparinization is recommended by the company, but this is left to the judgment of the individual therapist. Continuation of the antiplatelet regimen for at least 3 months is recommended, and serial radiographic follow-up is also necessary; however, poststenting imaging protocols have also not yet been established. Coding and billing of the implantation of the stent as an "embolization device" are similar to those for aneurysm coiling. In most instances, the stent (or multiple telescoping stents as is sometimes necessary) is adequate to achieve intra-aneurysmal thrombosis, but concomitant coiling is feasible with a jailed catheter before stent deployment because the pores will not permit passage of a microcatheter.

In this commentary, I wish to explore 3 issues regarding the PED: 1) reviewing the regulatory data leading to the introduction of this new endovascular device on the market, 2) training and credentialing for this new device and how an individual user and hospital can access the device for their patients, and 3) addressing where this new device falls in terms of judicious clinical use.

FDA approval for the PED device was granted after submission of data from the Pipeline for Uncoilable or Failed Aneurysms

(PUFS, unpublished) and the Pipeline Embolization Device for the Intracranial Treatment of Aneurysms (PITA) trials,[2] in addition to nonhuman and other smaller human studies. In the PUFS trial, 108 patients underwent attempted PED placement to treat wide-neck unruptured large aneurysms along the carotid segment from the petrous to the paraclinoid region between 2008 and 2009. Technical success was achieved in 107/108 aneurysms (99%). Of 364 PEDs used to treat these aneurysms, there was only 1 device failure. Ipsilateral major stroke or death occurred in 5.6% of patients. There was 1 death due to a delayed aneurysm rupture on day 14. Angiography performed at 180 days postdeployment demonstrated complete aneurysmal occlusion with <50% parent vessel stenosis in 73.6% of the studied cohort (99 subjects). In the PITA multicenter trial from Europe, 31 wide-neck unruptured aneurysms involving several different locations but, predominantly, the proximal internal intracranial carotid artery were treated with the PED. Mean aneurysm size was 11.5 mm, and 38.7% of lesions had undergone prior endovascular treatment. Technical successful deployment was demonstrated in 96.8% of cases, with 6-month angiographic aneurysm occlusion in 93% of patients. Two patients had periprocedural major strokes (6.5%), and there was no significant angiographic stenosis at 6 months.

There are currently no organizational credentialing standards for the placement of the PED, similar to neurointerventional training in general. The company, in conjunction with the FDA, has developed a set of criteria for clinical use, but the decision to allow an individual physician to place the PED lies squarely with the hospital administration once the criteria of the company are met. In the United States, to purchase and use the PED, the company mandates that any user attend a 1-day educational course, which includes hands-on PED deployment in a flow model. After that, the user must submit pictures on-line of intended cases meeting the previously described criteria selected by the manufacturing company: aneurysms measuring at least 10 mm in greatest dimension from the petrous to the superior hypophyseal location with wide necks measuring at least 4 mm in patients older than 22 years of age without any of the above-mentioned absolute contraindications. Cases are reviewed by a PED proctor hired by the company. If the adjudicator is satisfied that the case meets the criteria, the company coordinates a proctor to supervise the case. This process is the same for the first 5 cases for a given physician using the device. After those 5 cases, the next 5 cases, also meeting the above criteria, are attended by a nonphysician certified PED representative from the company. After those 10 cases are completed, the user may access the PED for use as he or she sees fit.

Since its rollout into the market, there has been a flurry of publications documenting use of the PED in myriad clinical situations, many off-label.[3-24] Complication rates, aneurysm occlusion rates, and in-stent stenosis rates with both short and intermediate follow-up have all been described, often with rates inconsistent with those reported in the premarket approval trials and quite disparate from 1 publication to the next.[8,21,25-32] This variability has not yet been accounted for. PED placement in patients harboring dissecting aneurysms, fusiform aneurysms, ruptured aneurysms, and saccular aneurysms of both the anterior and posterior circulation at sites other than the carotid petrous to superior hypophyseal internal carotid artery segments has been described. This use is not unexpected and reflects a somewhat disappointing and, I believe, backward way for new endovascular devices to be tested on humans. In the spirit of "I have a new device that is available to me and it might treat a lesion that I could not or would not otherwise treat," the PED has been used in a host of situations for which it did not garner FDA approval and for which there are precious few if any animal or human data to suggest safety or efficacy. Therefore, there is a very fine line between an operator believing that the natural history of the lesion untreated or treated with other available methods is so high that using a new device without a track record is justifiable and calling the treatment "assault and battery" of the patient. This subtle difference is not refereed by the company nor hospitals nor physicians themselves, and this inadequacy relates to the significance of "on-label" and "off-label" use, which is beyond the scope of this commentary. Be that as it may, we are left with a slew of ever-increasing publications by those brave enough to share their adventures and perhaps pleased enough with their results. We are plunged into this new world with the hope that we can get a better handle on the actual risks, benefits, and alternatives to using the PED in a given individual and without having to wait for a valid trial or recreate the same costly mistakes.

One of the newer complications encountered with the PED at a much higher rate than for non-PED endovascular therapy for unruptured aneurysms is intracranial hemorrhage, both aneurysmal and distant from the treated lesion, amounting to 0%–11% in variously reported series. The etiology of this complication is currently unknown, but the consequences for these patients who are typically on dual antiplatelet therapy are often disastrous. This type of complication is particularly unsettling, given our uncertainty of the dangers of an unruptured aneurysm compared with its ruptured counterpart, even for large, giant, or irregular lesions. The article by O'Kelly et al[1] is an important contribution to the literature in that it demonstrates that PED use for cavernous aneurysms carries a markedly lower rate of this dreaded complication; this article provides a good argument for using the PED for treating select cavernous lesions, which ironically already have a lower natural history. Noncavernous lesions, particularly lesions beyond the superior hypophyseal segment, should be treated with extreme caution and only after traditional approaches with better understood risk profiles have been exhausted and in cases in which there is a very strong probability that the risk of using the PED with its associated hemorrhage risk is lower than leaving the aneurysm alone. Unaddressed concerns regarding the use of PED include the following: duration of antiplatelet therapy, most appropriate imaging follow-up, cost-effectiveness relative to other potential treatment options, determination of the aneurysm, patient- or operator-specific factors that predispose these lesions to bleed posttreatment, long-term recurrence rate and in-stent stenosis rate, and when to complement stent placement with coiling.

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J.L. Brisman
Department of Neurosurgery
Winthrop University Hospital
Mineola, New York

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