Immediate and Midterm Results following Treatment of Unruptured Intracranial Aneurysms with the Pipeline Embolization Device

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Immediate and Midterm Results following Treatment of Unruptured Intracranial Aneurysms with the Pipeline Embolization Device

BACKGROUND AND PURPOSE: A number of flow-diverting devices have become available for endovascular occlusion of cerebral aneurysms. This article reports immediate and midterm results in treating unruptured aneurysms with the PED.

MATERIALS AND METHODS: A prospective registry was established at 3 Australian neurointerventional units. Aneurysms were treated on the basis of unfavorable anatomy or recurrence following previous treatment. Aneurysms were treated with PED or PED and coils. Data including antiplatelet therapy, technical issues, complications, and imaging findings were recorded during at least a 6-month period.

RESULTS: A total of 57 aneurysms in 54 patients were treated by 5 neurointerventional radiologists. Forty-one aneurysms were asymptomatic, and 16 patients had mass-induced neurological deficit. Clinical follow-up was available in 57 aneurysms with imaging follow-up at 6 months in 56. Permanent morbidity and mortality in the series was 0% at 6 months. Four TiAs and 1 small retinal branch occlusion occurred, but no stroke. The demonstrated aneurysm occlusion rate at 1 month was 61.9%, and the overall occlusion rate at 6 months was 85.7%. In cases previously untreated, the 6-month occlusion was 92.8%. Three of 6 aneurysms with a previous stent in situ were occluded. Two patients (3.5%) had asymptomatic in-construct stenosis of >50%. Acute aneurysm-provoked mass effect resolved or improved significantly in all cases.

CONCLUSIONS: Use of the PED is safe and efficacious in difficult aneurysms with a high occlusion rate at 6 months, but lower occlusion rates were seen in a small population with previous stents in situ.

ABBREVIATIONS: PED = Pipeline Embolization Device; PITA = Pipeline for the Intracranial Treatment of Aneurysms

The endovascular treatment of wide-neck aneurysms has been facilitated by the use of balloon remodelling and stent assistance, decreasing the recanalization rates that were seen with coiling alone. More recently, a number of flow-diverting devices have become available and are under evaluation. The PED (ev3, Irvine, California) is a self-expanding, microcatheter-delivered, 75% cobalt-nickel alloy, and 25% platinum mesh tube with 30%–35% metal surface coverage when fully deployed. Midterm results have been published recently in single-center registries and a multicenter international registry. All demonstrated that treatment of wide-neck aneurysms with PED reconstruction of the parent vessel was achieved safely. The purpose of this multicenter prospective registry was to analyze clinical experience as this flow diverter is released to the neurointerventional community and to assess whether the initial results can be generalized.

Materials and Methods

Patient Population
The study was a prospective case registry of all patients with lesions suitable for PED at 3 Australian neurointerventional centers between August 2009 and August 2010. Aneurysms with a wide neck (>4 mm), unfavorable dome/neck ratio (<1.6), a large (>10 mm), fusiform anatomy, and those that had failed previous therapy were selected. Each case was reviewed by a multidisciplinary team; before general release of the PED, individual application for use of the PED on compassionate grounds was sought from both hospital administration and the Therapeutic Goods and Services Administration. Written informed consent was obtained. Data were collected prospectively with respect to aneurysm morphology, symptoms, previous treatment, antiplatelet and anticoagulation regimens, and technical and clinical complications. Follow-up for at least 6 months evaluated occlusion, mass effect, delayed complications, ongoing antiplatelet therapy, and in-stent stenosis.

Antiplatelet and Anticoagulation Schedule
Antiplatelet protocols varied between operators. At 2 institutions, patients were pretreated with 75–150 mg daily of clopidogrel for 5 days. The latter dose has been shown to offer more reliable platelet inhibition. For at least 5 days before therapy, 100 mg (enteric coated) to 150 mg of daily aspirin was also given. If the mass effect symptoms were considered more urgent, patients were emergently loaded with clopidogrel (300–600 mg immediately) and 300 mg of aspirin before treatment. The higher 600-mg dose of clopidogrel is associated with more reliable levels of platelet inhibition. The other center chose to load patients with 300 mg of clopidogrel and 300 mg of aspirin for 2 days, based on previous coronary stent placement data. One center had access to a point-of-care platelet inhibition unit and could prescribe additional clopidogrel in patients with measured inadequate platelet inhibition.

Dual antiplatelet medication for 6 months was maintained in the
anterior circulation in accordance with the largest published PED experience. Dual agents were maintained in the posterior circulation for 12 months because this is a novel treatment with little published data on the incidence of perforator occlusion currently available. Patients were monitored for clopidogrel compliance by direct questioning. Aspirin therapy was prescribed life-long. All patients had intravenous heparin intraprocedurally with an activated clotting time of >200. Fifty-six of 57 patients had heparin infusion for at least 24 hours postprocedure (activated partial thromboplastin time, ×2 normal).

Procedure
Therapy was undertaken with the patient under general anesthesia. All PEDs were deployed by using high-magnification subtraction fluoroscopy through a Marksman (ev3, Irvine, California) 2.8F microcatheter. Initial experience with deployment involved a combination of unsheathing the device and pushing it out of the microcatheter. Additional PEDs were deployed at the discretion of the operator. Indications for multiple PEDs included inadequate neck coverage, fusiform aneurysm configuration, and an ongoing jet into the aneurysm. Ideally, stasis and a contrast/blood layer were observed at the cessation of the procedure. In some cases, coils were placed as part of the procedure before PED deployment or after jailing a microcatheter.

Discharge and Follow-Up
Elective patients were admitted on the day of the procedure and discharged at 36–72 hours, with CTA or MRA, if possible, 1 month posttreatment. A 6-month control angiogram was obtained and reviewed by 2 interventional neuroradiologists. Further angiography was performed if the aneurysm was open or in-construct narrowing was present. In patients with mass effect, MR imaging or CT was also performed if the aneurysm was open or in-construct narrowing was present. Clinical follow-up was performed at 1 and 6 months, in addition to independent evaluation by a neurologist or neurosurgeon. Patients were also seen more regularly if they had complex problems.

Study End Points
The primary end point was the angiographic appearance at 6 months with assessment of aneurysm closure and parent vessel stenosis. All clinical incidents (TIA, stroke, SAH, or mass effect) in the first 6 months posttreatment were documented. Secondary study endpoints included assessment of the influence of PED on symptomatic mass effect and aneurysm occlusion at 4 weeks by using MRA or CTA in as many patients as possible. A longitudinal study was undertaken beyond 6 months in patients with nonocclusion of the aneurysm (stopping clopidogrel at 6 months in the anterior circulation cases) or beyond 6 months in patients with nonocclusion of the aneurysm. In some cases, coils were placed as part of the procedure before PED deployment or after jailing a microcatheter.

Results

Patient and Aneurysm Characteristics
Data on 68 aneurysms in 65 patients were collected between August 2009 and August 2010. Eleven patients presenting with acute SAH were excluded and will be reported separately. This exclusion left 57 aneurysms in 54 patients for analysis. Forty-four women and 10 men (4.4:1) with a mean age of 55.7 years (median, 58 years; range, 30–83) and mean aneurysm size of 13.1 mm (median, 11 mm; range, 4–34 mm) were included.

Table 1: Size of aneurysm, number of PED, and use of coils

| Size         | No. | PED | PED | PED | Coils |
|--------------|-----|-----|-----|-----|-------|
| >25 mm       | 7   | 1   | 5   | 1   | 1     |
| 10–25 mm     | 32  | 16  | 11  | 5   | 2     |
| <10 mm       | 18  | 7   | 9   | 2   | 3     |
| Total        | 57  | 24  | 25  | 8   | 6     |

Table 2: Type, size, and occlusion rate of aneurysms

| Aneurysms (n = 57) | Berry (n = 46) | Fusiform (n = 11) | % Occluded at 6 Months |
|--------------------|---------------|------------------|------------------------|
| >25 mm (n = 7)     | 3             | 4                | 100.00                 |
| 10–25 mm (n = 32)  | 27            | 5                | 84.40                  |
| <10 mm (n = 18)    | 16            | 2                | 78.00                  |
| % Occluded at 6 months | 89.13       | 63.64            |                        |

Seven were giant (>25 mm); 32, large (10–25 mm); and 18, small (<10 mm). All 57 aneurysms had a neck width of >4 mm or an unfavorable dome/neck ratio of <1.6. Forty-six were berry and 11 were fusiform. Forty-six aneurysms were in the anterior circulation, and 11 were in the posterior circulation. Aneurysm characteristics are described in Tables 1 and 2.

Forty-one aneurysms were asymptomatic, and 16 patients had symptomatic mass effect with neurologic deficits. Sixteen patients had had prior treatment: 15 endovascular and 1 clipping. Four previously treated patients presented with symptomatic mass effect.

Treatment and Procedural Outcomes
Ninety-eight PEDs were placed in 57 aneurysms (1.72 per aneurysm). The PED was used as the sole treatment in 36 of 41 elective asymptomatic cases. Coils were placed in 3 elective cases. This choice was operator-dependent and was performed in the following scenarios:

1. A very wide-neck anterior communicating aneurysm in which the PED was protecting the A1/2 junction and narrowing, but not completely covering, the neck with secondary clipping via the opposite A1

2. A carotico-ophthalmic aneurysm with the ophthalmic artery coming out of the body of the aneurysm in an attempt to protect the retinal artery from embolism

3. A case converted to PED after initial partial clipping showed a neck wider than anticipated.

In the 16 cases with focal symptomatic mass effect, PED was used as the sole treatment in 13 cases with additional coils placed in 3 others due to the following:

1. An acute carotid cavernous fistula due to guidewire perforation successfully acutely with PED and coil deployment without sequelae.

2. A fusiform aneurysm in which the operator did not want to overlap the PED in the basilar trunk

3. An operator-based decision in a cavernous aneurysm, previously treated with coils.

Acute Procedural Technical and Clinical Complications
A poorly opened PED requiring angioplasty occurred in 1 case in which the PED did not fully open within an Enterprise stent (Cordis, Miami Lakes, Florida) (Figure 1). Persistent filling of the aneurysm required balloon angioplasty at 11 months with progressive aneurysm thrombosis evident at 18 months.
An acute carotocavernous fistula occurred in 1 patient during passage of a wire across a giant partly thrombosed cavernous aneurysm. The fistula was treated with coils and PED with no clinical consequence.

PED migration requiring additional treatment occurred in 2 cases. A 47-year-old man (Fig 2) had a 1-month post-PED implantation CTA demonstrating delayed proximal migration of the device, uncovering the aneurysm neck. Two additional PEDs were deployed the same day. Another patient had shortening of the distal PED, requiring placement of an Enterprise stent to anchor the PED.

Retroperitoneal hemorrhage occurred in 1 patient, requiring cessation of heparin infusion at 8 hours and 2 hours of packed cells. This settled with no other intervention.

**TIA, Stroke, and Death**

There were no cases in which thrombus was detected during the case and no cases of stent thrombosis. No deaths, strokes, or delayed-aneurysm rupture occurred. One acute TIA at day 2 and 3 delayed TIAs (2 at 3 months and 1 at 5 months) were recorded. All settled with clopidogrel reloading. One case with a multilobular carotico-ophthalmic aneurysm had a retinal branch occlusion, with no clinical sequelae, after jailed coiling of the locale from which the ophthalmic artery arose.

**Aneurysm Closure at Follow-Up**

Fifty-six of 57 aneurysms were available for imaging follow-up at 6 months. One other patient, living in a remote location, had ongoing clinical follow-up, with a 1- and 14-month CTA demonstrating 50% and 100% occlusion, respectively, with no stenosis.

**One-Month Imaging**

CTA, MRA, and, in 1 patient, DSA were performed at 1 month posttreatment in 31 patients (Table 3). Occlusion rates are summarized in Tables 2 and 3. Forty-eight of the 56 aneurysms imaged were occluded at 6 months (85.7%). In patients not previously treated, the occlusion rate was 92.5%. In 16 patients with prior treatment of the target aneurysm, the occlusion rate was 68.7%. In 50 patients with no stent in situ, the occlusion rate was 90%. Only 3 of 6 cases with previous stent in situ were occluded. A total of 8 aneurysms studied at 6 months (14.3%) remained patent. All patients were on dual
antiplatelet agents at that time. Clopidogrel has been stopped in all since then, with 2 further aneurysms occluding within 12 months.

In-Stent Stenosis
Two cases (3.5%) of in-stent stenosis of ≥50% were detected at 6 months. One (Fig 3) had long-segment intrastent 70% narrowing, decreasing to 30% at 12-month DSA. A second had 60% stenosis but had pre-existing mild narrowing of the parent vessel before PED. Both patients were ex-smokers, and 1 was noncompliant with clopidogrel. Both remain on dual antiplatelet therapy beyond 6 months, remaining asymptomatic.

Mass Effect
Sixteen patients presented with focal neurologic deficit from aneurysmal compression, 15 acutely and 1 with long-standing...
homonymous hemianopia. Eight were given 48 hours of steroi
d cover post-PED, and 3 had temporary symptom worsen-
ing, which resolved completely with time and longer steroi
d cover. Ten cases resolved within 1 month, and an additional 3,
in 1–6 months (Fig 4). Two had ongoing mild diplopia at 6
months but were markedly improved, with no change in the
patient with long-standing homonymous hemianopia.

**Discussion**

Large (>10 mm) wide-neck (>4 mm) aneurysms or those
with an unfavorable dome/neck ratio are more difficult to
treat and more prone to recurrence following endovascular
therapy. The development of flow diverters to reconstruct
vessels and occlude aneurysms has created much interest, and
recent single-center series and a multicenter registry show occlusion rates of 93%, 94%, and 93%, respectively, at 6-month follow-up. The PITA trial studied 31 aneurysms with no recent history of SAH; 71% were wide-neck (neck >4 mm or dome/neck ratio <1.5). Twelve (38.7%) had undergone previous endovascular treatment with coils or stent/coils. Dual antiplatelet therapy was maintained for a minimum of 30 days. Lylyk et al described a series of 63 aneurysms, without recent SAH; 67% were wide-neck (dome/neck ratio <2) or large, with 23 (37%) lesions previously treated. Dual antiplatelet medication was maintained for 6 months. Only 4 (6%) patients in the study of Lylyk et al were treated with PED and coils, whereas 16 (51.6%) were treated thus in the PITA trial. Our study population of 57 aneurysms all had morphology considered difficult to treat or with a greater likelihood of recurrence (neck >4 mm and/or dome/neck ratio <1.6). The size of our aneurysms (mean = 13.1 mm) also indicates a greater tendency to recurrence with conventional endovascular techniques.

The overall 6-month occlusion rate of 85.7% was lower in
our series compared with other series. In cases not previ-
ously treated, the occlusion rate was 92.9%, in line with pre-
vious results. All giant aneurysms were occluded. Eighty-nine percent of berry and 63.6% with fusiform morphology were
occluded at 6 months. In cases treated with no stent in situ, the
occlusion rate at 6 months for this series was 90% (45/50) and
at 14 months was 94.1% (48/51). These results compare with
balloon remodelling 77%–85% or stent-assisted tech-
niques,46%–74%. The presence of a stent in the vessel
results in a lower rate of occlusion, 50% in our small cohort of
6.

Our incidence of peri- and postprocedural complications
resulting in permanent morimortality was 0% in 57 cases of
asymptomatic aneurysms or those with mass effect. This com-
pares favorably with balloon-assisted coiling morbimortality of
3.75%–14.1%. There were no delayed ruptures in this
cohort. Rates of immediate procedural-related thromboem-
bolic stroke of 0% and 3.2% are also reported in other PED
series. This low published incidence should be compared with
2 reports on another flow diverter, Silk (Balt Extrusion, Mon-
tmorency, France), in which 4/13 cases had symptomatic
thromboembolic complications directly associated with the
procedure. A second article reported 15.4% (4/26) stroke
and 4% (1/26) mortality with a 33% in-stent stenosis rate in a
series of 26 patients in which the Silk flow diverter (Balt Extru-
sion) was successfully implanted in nonruptured aneu-
rysms. No intraprocedural thrombus or stent occlusion oc-
curred in our series or that of Lylyk et al, totalling 110 cases.
Byrne et al reported an 11% incidence of parent vessel throm-
bosis following Silk implantation in a series of 70 cases.

The literature has recently highlighted delayed rupture re-
lated to flow diverters in elective cases. Kulcsar et al doc-
umented 13 patients with delayed rupture following Silk use,
of which 2 may have had SAH. Rupture was defined as early
(2–48 days) in 10 patients or late (3–5 months) in 3 patients
who were no longer on dual antiplatelet therapy. Eleven pa-
tients had an inflow jet after flow-diverter insertion. In all
cases, it is our policy to insert the PED until any discernible
inflow jet is eliminated, if practicable. Cebral et al docu-
mented 13 cases of rupture following PED placement, all occur-
ring within 1 week of the procedure; 2 of these had stenosis
related to the parent vessel. Cebral et al highlighted the possi-
ble role of parent vessel stenosis in aneurysm rupture post-
PED, suggesting that coiling of these aneurysms may also be
required in that setting.

The possibility of delayed rupture, combined with animal
models demonstrating poor intraluminal organization of thombo-
sus at 3–6 months, despite cessation of dual antiplatelet
cover at 1 month, would favor a shorter period of clopi-
dogrel, perhaps 1–2 months. This recommendation needs to
be balanced against the risk of delayed stroke, though low,
with 5.3% having delayed TIA at 2- to 5-months after implan-
tation. If possible, we maintain dual antiplatelet cover for 12
months in implanted PEDs in the posterior circulation, be-
cause the treatment is novel at this time and the sequelae of
posterior perforator stroke are significant. However, we have 2
patients who stopped clopidogrel, at 1 week and 3 months,

| Table 3: Treatment devices and occlusion rates |
|-----------------------------------------------|
| **No Previous Aneurysm Treatment** | **Previous Treatment (Devices Inserted) Prior to PED** |
| Treatment PED Only or PED + coils | Coils | Stent or Stent/Coils |
| No. | 41 | 10 | 6 |
| Occluded at 1 month (n/z) | 19/31 | 6/7 | 1/4 |
| Occluded at 6 months (n/z) | 37/40 | 8/10 | 3/6 |
| % Occlusion at 6 months | 92.5% | 80% | 50.0% |
| No. not occluded at 6 months | 4 | 2 | 3 |
| No. subsequently occluded by 14 months | 3 |

**Note:** n indicates number of cases; z, number of cases imaged.

^3^ Three Enterprise, 1 coronary, and 1 Neuroform (Boston Scientific, Natick, Massachusetts).
with no clinical sequelae or stenosis. A case of delayed PED thrombosis was reported in the basilar artery at 2 years. The rate of in-stent stenosis was low in our series. This has been observed in animal models and in human series showing a 0%–4.8% moderate or severe rate of asymptomatic stenosis with clopidogrel maintenance of 1 and 6 months respectively. The degree of narrowing anecdotally diminishes with time when comparing 3- and 6-month angiograms. We had 1 patient in whom this was demonstrated. Acute mass effect at presentation was documented in 16 patients, with 3 having transient deterioration after PED deployment. None had permanent sequelae and responded with time and ongoing corticosteroids. No uniform policy is followed with respect to administration of steroids in large aneurysms, but patients must be observed for deterioration and ischemia must be ruled out by clinical evaluation and MR imaging, if necessary. In the 15 patients presenting with acute mass effect, symptoms resolved (n = 13) or markedly improved (n = 2) following PED implantation.

Deployment of the PED results in shortening of up to 50%–60%, depending on the size of the PED relative to the vessel and any discrepancy in proximal and distal vessel size. The device will tend to seek a larger lumen ("melon-seeding"), migrating proximally, if not well-expanded and anchored distally. As operator experience increased, the deployment technique changed, with more emphasis on distal vessel purchase and forward PED deployment, rather than unsheathing the device. In addition, axial reloading of the delivery catheter in the cavernous ICA is useful before the final portion of the PED is released. Nudging the proximal margin of the PED with the delivery catheter after deployment promotes proximal shortening of the PED. Anecdotally we believe this lessens potential shortening from the distal end, preventing proximal migration.

Conclusions
PED reconstruction of aneurysms with wide necks, unfavorable dome/neck ratio, and large size is safe, with high occlusion rates at 6 months and a low incidence of in-construct narrowing. The technique can be used in a wide variety of patients, and those with acute mass effect reliably responded to PED implantation. Adjunctive density coiling may be warranted in high-risk situations, such as stenosis in the parent vessel, by using the PED as a coil scaffold support rather than a flow diverter in selected suitable cases.

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Fig 4. A 62-year-old woman who presented with 2 days of increasing dysarthria, tongue weakness, and mild quadriparesis. A, T2-weighted axial MR image demonstrates a 30-mm aneurysm compressing the medulla and the fourth ventricle. B, Lateral DSA of the vertebrobasilar system shows a fusiform aneurysm of the proximal basilar trunk, incorporating the vertebrobasilar junction and the distal left vertebral artery. Two 2.75 × 18 mm PEDs overlapping in the sac were deployed into the basilar artery and left vertebral artery. Coils were placed in the distal right vertebral artery to stop an endoleak. The patient was placed on steroids but, 36 hours after treatment, had worsening of quadriparesis and developed bilateral ophthalmoplegia. MR imaging (not shown) did not completely demonstrate an infarct, and CTA (not shown) demonstrated exclusion of the aneurysm and patency of the PED. The patient was given an additional steroid bolus and recovered to normal health within 3 days. C, Six-month lateral left vertebral DSA demonstrates occlusion of the aneurysm with no stenosis. The coils in the right vertebral artery are visible as artifact. CT at 12 months (not shown) did not show a reduction in the size of the thrombosed aneurysm. Clopidogrel was ceased, and aspirin was continued. D, CTA at 18 months shows complete resorption of the aneurysm and absence of mass effect.
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