Long-term outcome of endovascular reconstruction with the Pipeline embolization device in the management of unruptured dissecting aneurysms of the intracranial vertebral artery

Clinical article


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Object. Use of a flow-diverting device has shown promising short-term results in the management of vertebral artery (VA) dissecting aneurysms, but there is still uncertainty regarding its long-term efficacy and safety. The authors report their initial experience with respect to the potential utility and long-term clinical outcomes of using a flow-diverting device in the treatment of unruptured dissecting VA aneurysms.

Methods. The authors conducted a retrospective review of all cases of unruptured intracranial VA dissecting aneurysms treated at their institution (Tuen Mun Hospital) with a flow-diverting device. They describe the clinical presentations and angiographic features of the cases and report the clinical outcome (with modified Rankin Scale [mRS] scores) at most recent follow-up, as well as results of the latest angiographic assessment, with particular focus on in-stent patency and side-branch occlusion.

Results. A total of 4 aneurysms were successfully obliterated by using flow-diverting devices alone. Two devices were deployed in a telescoping fashion in each of 2 aneurysms, whereas only 1 device was inserted in each of the other 2 aneurysms. No periprocedural complication was encountered. No patient showed any angiographic evidence of recurrence, in-stent thrombosis, or side-branch occlusion in angiographic reassessment at a mean of 22 months after treatment (range 18–24 months). As of the most recent clinical follow-up (mean 30 months after treatment, range 24–37 months), all patients had favorable outcomes (mRS Score 0).

Conclusions. Reconstruction using a flow-diverting device is an attractive alternative in definitive treatment of dissecting VA aneurysms, demonstrating favorable long-term clinical and angiographic outcomes and the ability to maintain parent artery and side-branch patency. It is particularly useful in cases with eloquent side-branch or dominant VA involvement.


Key Words • vertebral artery • dissecting aneurysm • flow-diverting device • Pipeline embolization device • vascular disorders

Dissecting VA aneurysms are now being recognized as a common cause of stroke and subarachnoid hemorrhage in young and otherwise healthy adults.19 The natural history of these lesions is uncertain, with variable evolution,25,29 but they are generally associated with high rates of morbidity and mortality, especially when complicated by rehemorrhage. Moreover, management of dissecting aneurysms of the intracranial VA remains controversial and lacks a standard protocol.4,5,19 Endovascular treatment has emerged as an alternative to surgical treatment and has shown promising results, with development of flow-diverting devices heralding a new era. It represents an attractive prospect, with the ability to reconstruct the parent VA making it a feasible alternative for patients who have dominant artery or major eloquent side-branch involvement with inadequate collateral flow. Nevertheless, uncertainty remains regarding its long-term efficacy and possible delayed complications, in particular thromboembolic events.

We report our initial experience with respect to the potential utility and long-term clinical outcomes of using a flow-diverting device as a sole treatment for unruptured dissecting VA aneurysms.
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Methods

We identified all cases of angiographically confirmed dissecting intracranial VA aneurysms treated at Tuen Mun Hospital with endovascular reconstruction. A total of 4 dissecting VA aneurysms in 3 patients were managed with flow-diverting devices. The patients were all men and were 48, 49, and 57 years old (mean 51.3 years). All 4 aneurysms were unruptured. Two patients (with 1 aneurysm each) presented with nonspecific headache. Two aneurysms were discovered as an incidental finding in the third patient after minor head trauma. The clinical status of the patients (presenting symptoms and Glasgow Coma Scale score) was recorded. Diagnostic digital subtraction vertebral angiograms were performed for definitive diagnosis in all cases and demonstrated fusiform dilation with or without pearl-and-string sign.

All patients were treated with the Pipeline embolization device (ev3 Inc.) as the sole endovascular intervention. Patients were premedicated with dual antiplatelet agents. All patients were administered a loading dose of clopidogrel (Plavix, 300 mg) 1 day before the procedure. Immediately before the procedure, after induction of general anesthesia, 3000 IU of heparin was administered intravenously. The VA was cannulated with a 6 Fr Neuron (Penumbra, Inc.) delivery catheter. Via a coaxial system, a microcatheter (Marksman, ev3 Inc.) was navigated to a point distal to the aneurysm under road-map guidance. The Pipeline embolization device (4.75 × 20 mm) was then introduced and deployed by a combination of forward pressure and retraction technique, with the goal of covering the aneurysm sac and diseased arterial segment. If there was unsatisfactory coverage of the aneurysm after placement of a single device, a second device would be inserted immediately in a telescoping fashion to augment support. A final angiogram was obtained at the conclusion of the procedure for confirmation of stent placement and patency. All patients were treated with dual antiplatelet therapy consisting of aspirin (100 mg) and clopidogrel (75 mg) daily for 3 months after the procedure. Clopidogrel treatment was then terminated; aspirin treatment was to be continued for life.

For the current study, the angiographic features of the lesions (morphology, relationship with the PICA, and VA dominance) and immediate outcomes were reviewed. Follow-up angiograms and MR imaging of the brain were examined to confirm the patency of the parent VA and eloquent side branches, as well as to identify any newly developed infarct in the posterior circulation territory. The long-term clinical outcomes were analyzed on the basis of the mRS scores at the most recent follow-up examination.

Results

Initial diagnostic vertebral angiograms confirmed the presence of dissecting aneurysms in the distal intradural portion of the VA in all 3 patients. Equal involvement of both the right (2 lesions [50%]) and left (2 lesions [50%]) VA was observed, with 1 patient having bilateral involvement. One aneurysm (in Patient 1) was located in the dominant VA, while the remaining 3 aneurysms (in Patients 2 and 3) were located in codominant VAs. All 4 aneurysms were located distal to the origin of the PICA. The patients’ demographic characteristics, clinical data, treatment, and outcomes are summarized in Table 1.

Treatment was technically successful without peri- or intraprocedural complication in all patients (Figs. 1–4). Two Pipeline embolization devices were deployed in each of 2 aneurysms (in Patient 1 and in the left VA in Patient 3) due to inadequate support and coverage of the aneurysm after initial deployment of the first device. Only a single Pipeline embolization device was deployed for each of the remaining two. In Patient 3, the origin of the PICA at the left VA had to be covered by the device due to close proximity to the aneurysm (Fig. 4A). The rest of the PICAs and all of the anterior spinal arteries were safeguarded in the remaining VAs. Postprocedure angiograms revealed satisfactory positioning of the devices with immediate reduction of flow into the aneurysm sac and stagnation of contrast medium (Fig. 4B). The left PICA remained patent in Patient 3.

All 3 patients remained well after the procedure with no focal neurological deficit. Follow-up MR imaging of the brain performed at 6–18 months after the procedure did not reveal any infarct along the posterior circulation territory. The most recent digital subtraction angiograms (performed at 18–24 months posttreatment) confirmed complete obliteration of the aneurysms with preservation of the parent VA and eloquent side branches (Fig. 4C). No angiographic recurrence was found. All patients remained well and asymptomatic (mRS Score 0) throughout clinical follow-up (mean 30 months, range 24–37 months), with no clinical sign or symptom of stroke.

### TABLE 1: Summary of demographic and clinical characteristics, treatments, and clinical outcomes in 3 patients*

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (yrs), Sex</th>
<th>Presentation</th>
<th>SAH Side</th>
<th>VA Dominance</th>
<th>Location</th>
<th>Type of Treatment</th>
<th>FU (mos)†</th>
<th>mRS Score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48, M</td>
<td>headache</td>
<td>no</td>
<td>lt</td>
<td>distal-to-PICA</td>
<td>Pipeline × 2</td>
<td>24</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>49, M</td>
<td>headache</td>
<td>no</td>
<td>rt</td>
<td>distal-to-PICA</td>
<td>Pipeline × 1</td>
<td>24</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>57, M</td>
<td>incidental</td>
<td>no</td>
<td>lt</td>
<td>distal-to-PICA</td>
<td>Pipeline × 2</td>
<td>18</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

* DSA = digital subtraction angiography; FU = follow-up; Pt = patient; SAH = subarachnoid hemorrhage; VA = vertebral artery.
† Length of time from treatment to most recent imaging and clinical follow-up.
The natural history of dissecting aneurysms of the VA is unclear, and management strategies remain controversial and individualized. Conservative management with anticoagulation therapy was initially adopted for unruptured dissecting VA aneurysms, as these lesions were thought to be associated with a benign clinical course and outcome, arguing against the need for invasive treatment. However, Coley and Clifton and Naito et al. subsequently demonstrated that the risk of bleeding from unruptured dissecting VA aneurysms was higher than previously thought, and Jin et al. demonstrated favorable clinical outcomes with endovascular intervention in patients with unruptured vertebrobasilar aneurysms, supporting the argument for definitive treatment of unruptured lesions. In contrast, it has been widely accepted that ruptured VA aneurysms should definitely be treated immediately due to a high mortality rate of up to 50%. Direct surgical repair is often technically demanding and associated with high rates of morbidity and mortality, and endovascular treatment in the form of parent artery occlusion or intracranial stenting has shown promising results. Parent artery occlusion remains the best and most reliable technique for definitive obliteration of the aneurysm, but may not be feasible for cases with dominant artery or major branch (PICA or anterior spinal artery) involvement without adequate collateral flow. Scarification of the PICA is not always as dangerous as one might think, because of the presence of rich pial anastomoses, but occlusion of the anterior spinal artery can be devastating and remains a major concern. Balloon test occlusion can be valuable in helping to assess the adequacy of collateral circulation and cortical flow, but it is not always reliable, and the final decision of parent artery occlusion remains a clinical one.

Fiorella et al. believe that cerebral aneurysms represent a response to deleterious shear stress and pathological blood flow patterns in the vessel wall, such that remodeling of cerebral blood flow is beneficial and seems to be more appropriate than aneurysm sac occlusion. Reconstruction by means of endovascular stent placement represents an important advance in the ongoing development of endovascular remodeling strategies for aneurysm treatment, demonstrating favorable results in recent studies. The Neuroform and Enterprise stents were initially developed specifically for use in cerebral arteries, but they were designed to be used primarily as adjunctive treatments to provide structural support for coil embolization of cerebral aneurysms. The limited metal surface area of these stents does not allow their use as reliable stand-alone therapy for the majority of intracranial aneurysms. The use of covered stents has been proposed, but was limited by their restricted flexibility and the inevitable occlusion of important side branches.

The Pipeline embolization device was recently introduced as the first flow-diverting device intended to hemodynamically exclude aneurysm from parent artery as a primary treatment. Although the procedure itself is technically demanding, it is in general safer than coil embolization due to elimination of the risks entailed in direct manipulation of the aneurysm sac with the microcatheter and coil mass. It is designed to achieve endoluminal remodeling by enhancing flow diversion and re-
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Reducing inflow and outflow jets from the aneurysm, hence promoting progressive intrasac thrombosis.\textsuperscript{9,24,28} It also acts as a stimulus to provide scaffolding in supporting neointimal overgrowth across the aneurysm neck defect, thereby facilitating biological remodeling. Its enhanced metal surface area coverage (a 3- to 5-fold increase over the Neuroform stent) allows satisfactory aneurysm occlusion,\textsuperscript{24,28} and coverage can be increased by placing multiple devices in a telescoping fashion. This device has a distinct advantage in providing immediate flow diversion compared with non–flow-diverting stents, which rely primarily on neointimal response, and more rapid aneurysm thrombosis can thus be achieved. The Pipeline embolization device is also particularly useful in eliminating aneurysm remnants, which are not uncommonly encountered after coil embolization but are difficult to treat with additional coil placement. All 3 patients treated by means of the Pipeline embolization device in our series demonstrated successful obliteration of the aneurysms and favorable long-term clinical outcomes with an mRS score of 0 on most recent follow-up. No clinical or angiographic evidence of recurrence or rebleeding was found with a mean clinical follow-up period of 30 months and a mean angiographic follow-up period of 22 months.

Although this device is exciting and promising, it has a major disadvantage of preventing access to the aneurysm after its deployment due to its small pore size,\textsuperscript{9} causing some reluctance to use this device as stand-alone therapy. The long-term patency and thromboembolic risk, especially when multiple devices are used, has yet to be determined. The possibility of complicated in-stent thrombosis due to intimal hyperplasia with thrombus propagation to distal branches and perforating vessels is a major concern.\textsuperscript{32} Strict compliance with dual antiplatelet therapy both before and after the procedure is mandatory for prevention of this devastating complication. There is no consensus as to when the antiplatelet medications can be withdrawn. We adopted a regimen of a single bolus loading dose of clopidogrel (300 mg) on the day before the procedure, followed by aspirin (100 mg) and clopidogrel (75 mg) daily for 3 months after the procedure. Clopidogrel could be withdrawn after completion of this 3-month posttreatment regimen, with daily aspirin therapy being continued as a lifelong regimen. Nevertheless, late in-stent thrombosis (more than 1 year posttreatment) has been reported.\textsuperscript{8,10} In particular, Fiorella et al.\textsuperscript{8} reported a rare case of very late thrombosis of the Pipeline embolization device 2 years after placement, leading to a posterior circulation stroke. In this case, the dual antiplatelet regimen was of a higher dose (325 mg aspirin and 150 mg clopidogrel daily) and longer duration (clopidogrel was continued for 12 months) than our regimen. However, the authors acknowledged that the patient was probably suffering from underlying vasculopathy, resulting in this unusual, very late in-stent thrombosis. Although this is a single isolated case, it highlights the need for a larger trial with longer follow-up to ascertain the safety of this treatment. Attention must be paid to the dual antiplatelet regimen, which may need to be individualized. Other potential complications include delayed aneurysm rupture from thrombus-associated autolysis of the aneurysm wall.\textsuperscript{24}

![Fig. 3. Patient 3: right VA aneurysm. Left: Pretreatment right vertebral arteriogram showing a dissecting aneurysm at the distal intradural portion of the right VA. Right: Follow-up angiogram obtained 18 months after placement of a Pipeline embolization device, demonstrating complete obliteration of the aneurysm with a patent parent artery.](image)

![Fig. 4. Patient 3: left VA aneurysm. A: Pretreatment left vertebral arteriogram showing a dissecting aneurysm at the distal intradural portion of the left VA with close proximity to the PICA. B: Left vertebral arteriogram obtained immediately after placement of 2 Pipeline embolization devices, demonstrating satisfactory positioning of the devices with immediate reduction of inflow into the aneurysm sac and stagnation of contrast medium (arrow). C: Follow-up left vertebral arteriogram obtained 18 months after treatment, demonstrating patency of the covered PICA (arrow) with complete obliteration of the aneurysm.](image)
Another important consideration is the maintenance of patency of branch vessels or perforators from the parent vessel. Theoretically this is possible due to the presence of interstices between the stent strands. However, there have been mixed results, with cases of branch artery occlusion being reported. Cross-PICA coverage for stent placement in the left VA was necessary in Patient 3 in our case series for adequate exclusion of the aneurysm. The artery was still patent on the most recent follow-up angiogram, and there was no evidence of the patient having had a complicated cerebellar/brainstem infarction or stroke episode on latest clinical follow-up. Despite this initial favorable result, further long-term follow-up is clearly of particular importance in this case.

Conclusions

Reconstruction using a flow-diverting device is an attractive alternative in definitive treatment of dissecting aneurysms of the VA, showing favorable long-term clinical and angiographic outcomes with the ability to maintain parent artery and side-branch patency. It is particularly useful in patients with eloquent side-branch or dominant VA involvement.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lai, Yeung, Wong. Acquisition of data: Yeung, Lau. Analysis and interpretation of data: Lai, Lau, Poon, Tan. Drafting the article: Lai, Yeung. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lai. Statistical analysis: Lau, Poon. Administrative/technical/material support: Tan, Wong. Study supervision: Tan.

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