ORIGINAL ARTICLE

Pipeline embolisation device for wide-necked internal carotid artery aneurysms in a hospital in Hong Kong: preliminary experience

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Objective To review our hospital's experience with the pipeline embolisation device to reconstruct wide-necked intracranial aneurysms.

Design Descriptive case series.

Setting A regional neurosurgical centre in Hong Kong.

Patients Patients presented with wide-necked intracranial internal carotid artery aneurysms who underwent pipeline embolisation device reconstruction between October 2008 and June 2009.

Results There were 13 wide-necked internal carotid artery aneurysms (in nine patients) treated by pipeline embolisation device reconstruction. Eleven aneurysms were de-novo; two were recurrent. The complete occlusion rate was 66% (8/13) at the first angiographic follow-up and 69% (9/13) at the second follow-up. One patient developed in-stent stenosis and in another there was distal migration of the stent. There was no added neurological deficit in any patient.

Conclusion In our series, the clinical results from using the pipeline embolisation device for the treatment of non-ruptured internal carotid artery aneurysms appeared encouraging. However, larger studies with longer follow-up duration are warranted to assess the complications and durability of the device for reconstructing internal carotid artery aneurysms.

New knowledge added by this study

- The preliminary experience, data, and difficulties encountered using the pipeline embolisation device (PED) in a Hong Kong hospital are described.

Implications for clinical practice or policy

- The study facilitates review of important clinical points when considering PED as the treatment for intracranial aneurysms.

Introduction

In recent years, a new-generation microstent, the pipeline embolisation device (PED), has been developed. This is a flexible, microcatheter-delivered, self-expanding, endovascular 'stent-like' construct that is a 'standalone' device for the treatment of non-ruptured cerebral aneurysms. The device is composed of 48 individually braided cobalt chromium and platinum strands, which provide a 30 to 35% metal surface area when fully deployed. It differs from other commercially available self-expanding intracranial microstents that are currently in routine use. Fundamentally, the latter stents produce endosaccular occlusion of the targeted cerebral aneurysm. By contrast, the PED is designed to provide a larger surface across the neck of the aneurysm, which therefore becomes excluded from the circulation and allows a physiological reconstruction of the diseased parent vessel (parent vessel reconstruction). Meanwhile, the patency of any branch vessels being covered by the PED is preserved as the device is porous enough to maintain a sufficient blood flow across it, flow being driven by the pressure gradient between the parent artery and the low pressure venous system. The resulting blood flow maintains the patency of parent vessels and governs the endothelisation process.[1-3]

Here we present our experience in a local neurosurgical centre in Hong Kong (Department of Neurosurgery, Kwong Wah Hospital) during the period 27 October 2008 to 15 June 2009.

Key words
Blood vessel prosthesis implantation; Embolization, therapeutic; Intracranial aneurysm; Neurosurgical procedures; Reconstructive surgical procedures

Hong Kong Med J 2011;17:398-404

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Methods

Within the period from 27 October 2008 to 15 June 2009, there were nine patients (7 female and 2 male) treated with PEDs for internal carotid artery aneurysms (Table 1). Their ages ranged from 39 to 76 (mean, 57) years. The study was a retrospective, all-inclusive case series of patients undergoing PED reconstruction of wide-necked aneurysms. All these aneurysms were considered as difficult-to-treat by coiling with adjunct devices.

Clopidogrel 75 mg daily was prescribed to all patients 3 days prior to procedure and continued for 6 more months thereafter, aspirin 80 mg daily was prescribed on case-by-case basis. We adopted an antiplatelet regimen that differed from published series based on the assumption that our Chinese patients have a relatively lower thromboembolic risk than the non-Chinese. Intravenous heparin was administered during the procedure and 1 day after; the activated partial thromboplastin time being maintained between 2 and 3 times the upper limit of normal. Heparinisation was not reversed after completion of its administration.

Patients were followed up by two sessions of digital subtraction angiography (DSA). Complete occlusion was defined as no contrast material entering the aneurysm. One patient had one session of follow-up (FU) DSA replaced by a computed tomography angiogram. The first session of DSA was performed after a mean interval of 4 months (range, 2-6 months) and the second session was performed after a mean interval of 14 months (range, 10-15

管道栓塞器治療寬頸內動脈瘤：香港一所醫院的初步經驗

目的 回顧使用管道栓塞器治療顱內寬頸動脈瘤的經驗。

設計 描述性病例系列。

安排 香港一所分區腦外科中心。

患者 2008年10月至2009年6月期間因顱內寬頸動脈瘤接受管道栓塞器治療的病人。

結果 共有13名因顱內寬頸動脈瘤接受管道栓塞器治療的病人，其中11人為首發動脈瘤，其餘兩人屬復發性動脈瘤。第一次血管造影隨訪時的完全閉合率為66%（8/13），第二次隨訪的完全閉合率則為69%（9/13）。其中一人出現動脈支架內狹窄，另一人有支架移位。所有病人均無神經功能缺損。

結論 本院使用管道栓塞器治療無破裂顱內寬頸動脈瘤的結果令人鼓舞。儘管如此，仍須進行更多大型及長時間隨訪的研究，以探討用作治療顱內寬頸動脈瘤的管道栓塞器的耐用性及是否會引致併發症。

TABLE 1. Patient profile*

Patient No.	Sex/ age (years)	Presentation	Aneurysm site (ICA)	Size (mm)	1st FU DSA (interval)	2nd FU DSA (internal)	Complication	GOS	No. of stents across aneurysm
1	F/64	Previously treated aneurysm	Rt ophthalmic	15 x 20	Residual 13.4 x 16.7 mm ; 5 m	Residual 11.7 x 16.3 mm; 10 m	Stent migration	5	2
2	M/52	Right hemianopia	Rt ophthalmic	5 x 5	Complete occlusion; 2 m	Complete occlusion; 15 m	-	5	1
3	F/75	Incidental MRI finding	Lt ophthalmic (parasellar)	20 x1.5	Residual 5 x 3 mm; 3 m	Complete occlusion; 13 m	-	5	2
4	F/39	Previously treated aneurysm	Rt communicating	10 x 16	Residual 6 x 3 mm; 6 m	Residual 6 x 3 mm; 13 m	-	5	2
5	F/61	Headache	Rt cavernous	3.5 x 3	Complete occlusion; 5 m	Complete occlusion; 12 m	-	5	2
			Lt cavernous	3.5 x 2.2	Complete occlusion; 5 m	Complete occlusion; 12 m			1
6	F/42	Headache	Lt ophthalmic	3 x 2	Complete occlusion; 5 m	Complete occlusion; 12 m	-	5	1
			Lt cavernous (anterior genu)	3 x 2.5	Complete occlusion; 5 m	Complete occlusion; 12 m			1
			Lt cavernous posterior genu)	2.5 x 2	Complete occlusion; 5 m	Complete occlusion; 12 m			1
7	M/51	Dizziness	Rt ophthalmic	2 x 2.5	Complete occlusion; 3 m	Complete occlusion; 12 m	In-stent stenosis	5	1
8	F/54	Headache	Rt cavernous	6.3 x 3.7	Residual 1.5 mm; 4 m	Complete occlusion; 12 m	-	5	2
			Rt ophthalmic	6.3 x 2.5	Residual 4 x 2 mm; 4 m	Residual 4 x 2 mm; 12 m			2
9	F/76	Headache	Lt cavernous	9 x 7.4	Residual filling (CT); 3 m	Residual 3 x 1 mm; 12 m	-	5	1

* CT computed tomography, FU DSA follow-up digital subtraction angiography, GOS Glasgow Outcome Scale score, ICA internal carotid artery, Lt left, MRI magnetic resonance imaging, and Rt right

months). Glasgow Outcome Scale (GOS) scores and possible complications were assessed at clinical FU.

Embolisation techniques

All PED embolisation procedures were performed under general anaesthesia using a biplane angiographic unit. After setting the working projections, a 0.027-inch inner lumen Marksman microcatheter (ev3 Neurovascular; Chestnut Medical, Menlo Park [CA], US) was manipulated with the aid of a pre-shaped micro-guidewire under high-magnification fluoroscopic roadmap control beyond the aneurysm neck. The micro-guidewire was preferentially positioned at one of the major branches of the middle cerebral artery. The tip of the micro-guidewire was then withdrawn. The PED, mounted on a delivery wire and constrained within a sheath, was then inserted into the rotating haemostatic valve and introduced into the hub of the microcatheter. By pushing the delivery wire, the PED was advanced through the length of the microcatheter to reach the appropriate position for deployment. A radio-opaque short floppy segment of the delivery wire was used to determine the distal anchorage position of the PED. The delivery wire was then held in place while the microcatheter was carefully retracted to expose one third of the length of the PED before deployment. While keeping the position of the microcatheter in place, the delivery wire was pushed forward to deploy more of the PED into the vessel lumen. Under fluoroscopy, the PED formed an olive shape after engaging the sidewall of the vessel. By rotating the delivery wire clockwise with the aid of a torquer device, the distal end of the PED was released. Once its distal end was freed, PED deployment was continued through a combination of forward pressure on the delivery wire and retraction of the microcatheter until the proximal marker of the PED was reached. During this stage of manoeuvre, the position of the distal floppy end of the delivery wire was constantly checked to avoid undesirable distal migration into a small vessel. Once the PED expanded to become free of the delivery microwire, the microcatheter was pushed forward to retrieve the delivery wire whilst also ensuring complete release of the proximal end of the PED. When constrained within a microcatheter, the PED elongates 2.5 times to attain its maximally expanded deployed configuration. This foreshortening must be taken into account during the positioning and deployment of the construct. Unlike an ordinary stent, the deployment mechanism allows longitudinal compression of the PED across the neck of the aneurysm, thus reducing porosity at that segment. If two PEDs were to be deployed coaxially, the first PED was unsheathed normally to serve as scaffolding while the second PED with a smaller diameter was 'packed' tightly to reduce porosity. Such measures prevented prolapse of the PED into the aneurysm with a wide neck or fusiform in shape.

Results

Clinical results

Functionally, patients were graded according to the GOS. The GOS scores of all patients were graded as 5 in pre-PED deployment, post-PED deployment, and subsequent 12-month FU assessment. No added focal neurological deficit was noted within the 12-month period of FU, nor was there any major peri-procedural complication (death, major stroke).

Angiographic results

There were 13 wide-necked aneurysms (neck >4 mm or dome-to-neck ratio <2) in these nine patients; 11 were de-novo; two were recurrent and had been previously treated, one by coil embolisation and one by clipping. All the aneurysms were located in the

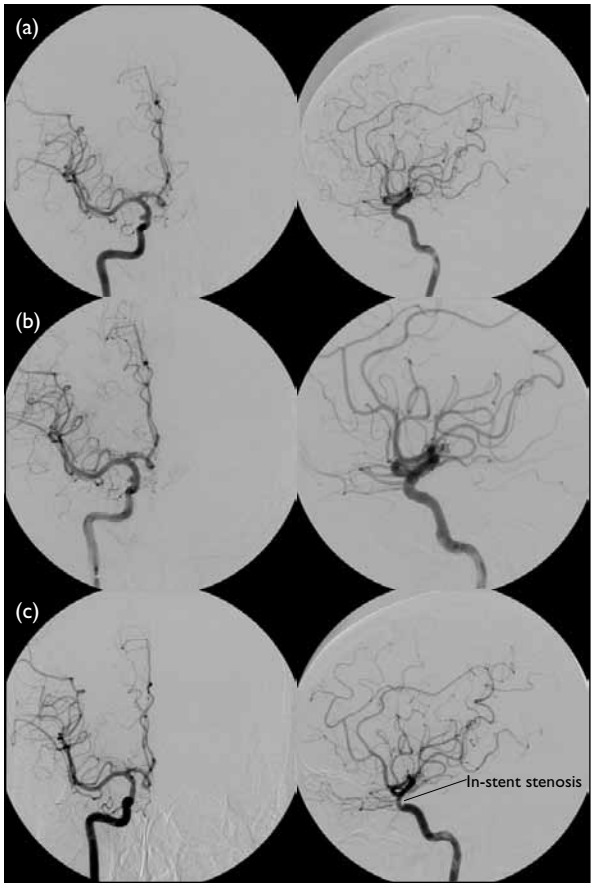

FIG 1. Case of in-stent stenosis
(a) Anteroposterior and lateral view of pre-embolisation digital subtraction angiography (DSA) showing a laterally pointing right supraophthalmic artery aneurysm. (b) Anteroposterior and lateral view of immediate post-embolisation DSA. (c) 3-Month follow-up DSA shows early in-stent stenosis with reduced luminal diameter from 4.39 mm (proximal-to-stent segment) to 2.77 mm (in-stent). The maximum thickness of intimal hyperplasia is found to be 1 mm

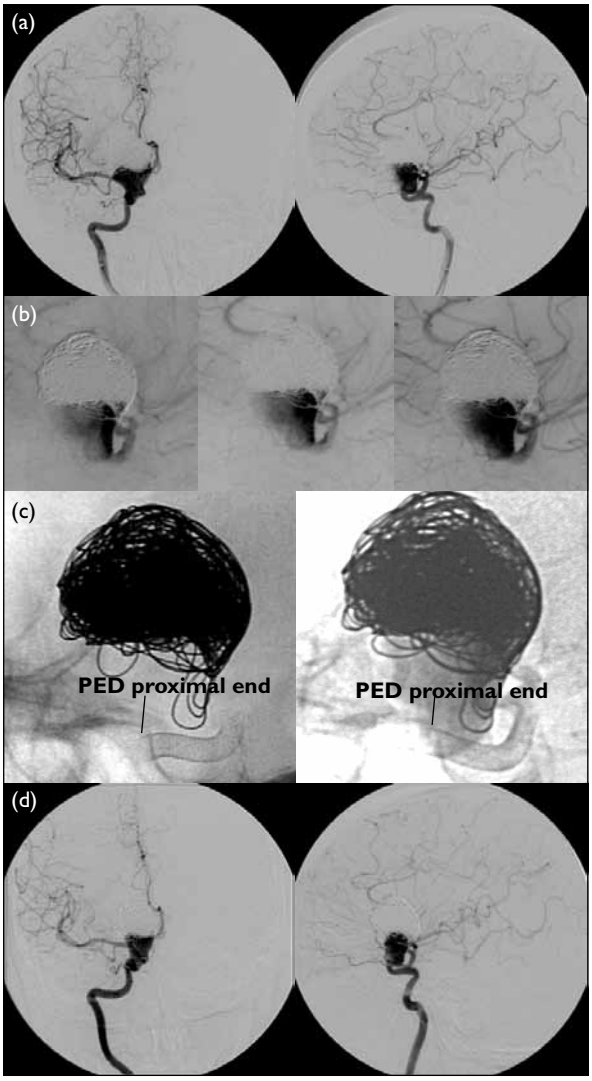

FIG 2. Case stent migration distally
(a) Anteroposterior and lateral view of the immediate post–pipeline embolisation device (PED) embolisation digital subtraction angiography (DSA) for a previously coiled giant aneurysm (27 x 25 mm). (b) Contrast stasis immediately after PED deployment. (c) Native film immediately after PED deployment and 6 months after showing stent distal migration. (d) Follow-up DSA at 1 year shows mild shrinkage of the residual aneurysm

internal carotid artery. According to the International Study of Unruptured Intracranial Aneurysms (ISUIA)[4] classification, 10 were small (<10 mm), three were large (10-25 mm) and none was giant (>25 mm). Regions of the aneurysm that were occluded by pre-existing embolisation coils or intraluminal thrombus were not included in the largest dimensional measurement. They arose from cavernous segment (n=6), the ophthalmic segment (n=6), and the communicating segment (n=1) of internal carotid artery.

To treat these nine patients, 15 PEDs were deployed for these 13 aneurysms. The average number of stents per aneurysm was 1.15; seven being treated with a single PED, and for six, two overlapping PEDs were deployed (Table 1). All the PEDs were deployed successfully in the pre-determined position during a single interventional DSA session. No branch vessel was obliterated. The complete occlusion rate was 62% (8/13) at the first angiographic FU and 69% (9/13) at the second FU. One of the residual aneurysms (in patient No. 8) noted in the first DSA study became completely occluded in the second study. All the aneurysms showed endosaccular contrast stasis immediately after PED deployment.

There was one patient that endured in-stent stenosis (Fig 1; patient No. 7) and one in whom there was distal migration of the stent (Fig 2; patient No. 1).

Case illustrations

A 75-year-old woman complained of deterioration of left eye vision for 1 year. Magnetic resonance imaging showed a pituitary tumour and an unruptured, cavernous segment, internal carotid aneurysm. Digital subtraction angiogram showed a left parasellar 20 x 15 mm wide-necked large aneurysm (Fig 3a). Two overlapping PEDs were deployed across the aneurysm neck. The eclipse sign was seen immediately after PED deployment (Fig 3b). At the 1-year DSA FU, there was complete occlusion of the aneurysm and no in-stent stenosis (Fig 3c). Clinically, after the pipeline embolisation there was no added

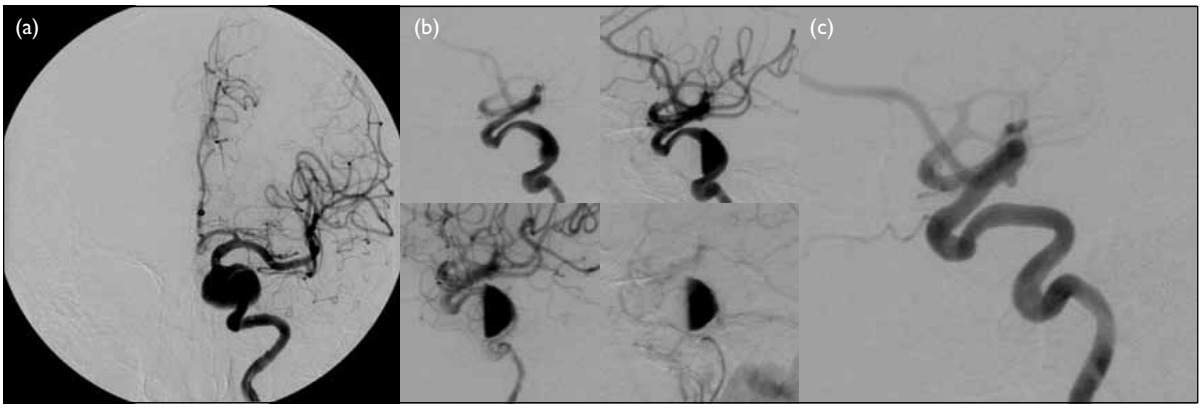

FIG 3. (a) Pre-embolisation digital subtraction angiography (DSA). (b) Immediate post-embolisation DSA showing eclipse sign. (c) One-year follow-up DSA showing complete occlusion of aneurysm

TABLE 2. Peri-procedural complications reported in overseas large case studies[3,5,6]

Study	No. of major complications (major stroke or death)	Major complications
PITA trial[5]	2/31 (6%)	1 Large left hemisphere stroke 1 Right-sided hemiparesis and motor aphasia
The Buenos Aires experience[3]	0/53 (0%)	
The Budapest experience[6]	1/19 (5%)	1 Diffuse subarachnoid haemorrhage, patient died

neurological deficit. The patient's GOS score remained at 5. The pituitary tumour was treated using a Gamma knife, 4 months after pipeline embolisation of the aneurysm. She noted subjective improvement of vision in her right eye.

Discussion

Treatment for small, unruptured cerebral aneurysms

The treatment for a small, unruptured cerebral aneurysm (<10 mm) is still controversial. Especially for small-sized aneurysms (<10 mm), when considering patient selection for PED reconstruction, it is paramount to compare procedural risks, long-term complication risks, and the aneurysm rupture risks. The risk of PED reconstruction must not outweigh the risk of conservative management (risk of aneurysm rupture).

Complication risks of pipeline embolisation device reconstruction

Since the PED has become commercially available only in the recent few years, the long-term risk of complications is still uncertain. Peri-procedural complications have been reported in three large case studies from overseas (Table 2[3,5,6]).

Other peri-procedural complications resulting in mild or transient neurological deficits were also reported, and included transient vasospasm, transient mild hemiparesis, acute intra-procedural in-stent thrombosis (due to omission of antiplatelet medication) and embolic occlusion of the retinal artery causing a small visual field defect.[6]

Conservative management

The ISUIA[4] carried out in Canada, the US and the Europe suggested that the risk of rupture, particularly aneurysms smaller than 7 mm and those in the anterior circulation, is extremely small (0.05% per year), and the 5-year cumulative risk of rupture was 0% in the group studied prospectively. Another systematic review carried out by Rinkel et al[7] in 1997 reviewed nine studies (3907 patient-years of FU) which yielded an overall rupture risk per year of 1.9% (95% confidence interval, 1.5-2.4); for aneurysms of 10 mm or smaller, the annual risk was 0.7% (95% confidence interval, 0.5-1.0). Notably, according to currently available reports, the risk of rupture for small aneurysms varies considerably, and the majority refer to non-Chinese or even non-Asian populations. A local study suggested that Chinese patients in Hong Kong with intracranial aneurysms tended to present with subarachnoid haemorrhage at an earlier stage, and therefore the lesions tended to be smaller.[8]

To date, there is no consensus on the indication for PED reconstruction for patients with intracranial aneurysms in Hong Kong. When considering PED for intracranial aneurysm treatment, a detailed patient-specific discussion to explain benefits and risks with up-to-date evidence is definitely warranted. Other treatment modalities like coiling and clipping, together with conservative management, should also be taken into consideration. The fact that the PED is still an investigational device and its long-term results not yet being available should be emphasised.

Complete occlusion rate

Published clinical data have shown a satisfactory complete occlusion rate for aneurysms treated by PED (Table 3[3,5,6]). The complete angiographic occlusion rate approaching 93 to 94% in the 6-month post-procedure FU study has been demonstrated in the three large-scale studies (The PITA trial,[5] The Budapest experience,[6] and The Buenos Aires experience[3]). Our series showed a relatively lower complete occlusion rate of 62% (8/13) at the 4-month FU and 69% (9/13) at the 12-month FU.

In our series, no aneurysm demonstrated recanalisation during the study period, which was also noted in the aforementioned three large-scale studies. For this reason, we consider the PED to be a more promising and durable means of treating intracranial aneurysms than conventional coiling. In fact, local data suggested that only 87% (67/77) of aneurysms that are completely occluded by coil embolisation initially, remain totally occluded at the 18-month FU DSA.[8]

Patency of branch vessels

The patency of branch vessels covered by PEDs is an important safety issue. In our case series, no branch

TABLE 3. Complete occlusion rates[3,5,6]

Study	Complete occlusion rates (months after pipeline embolisation device embolisation)
Present series	62% (4); 69% (12)
The Buenos Aires experience[3]	35% (1); 56% (3); 93% (6); 94% (12)
PITA trial[5]	93% (6)
The Budapest experience[6]*	94% (6)

* Nine patients were treated in PITA trial which enrolled a total of 31 patients, including the data from these nine patients, the complete occlusion rate is 94% (17/18), one patient dropped out as the patient died

vessel was noted to be occluded, whilst clinically, there was no neurological deficit at the 12-month FU. Theoretically, any vessels with a collateral flow from the external carotid artery may create a 'flow equalisation point'. For example, the deployment of a PED covering the ophthalmic artery opening may result in slow flow or occlusion in the ophthalmic artery.[2] Szikora et al[6] have reported two ophthalmic arteries, each covered by three or four PEDs that were found to have undergone clinically silent occlusion at the 6-month FU. Another condition reported in the PITA trial[5] involved a patient who experienced a peri-procedural stroke manifesting as a right-sided hemiparesis and motor aphasia following reconstruction of the M1 segment of the left middle cerebral artery with two overlapping PEDs and a neuroform stent followed by coil embolisation of a giant M1 aneurysm. The authors considered this event attributable to the covering of regional lenticulostriate branches with multiple PEDs.

In our series, six ophthalmic arteries were covered by PEDs. However none of the patients developed ophthalmic artery occlusion or stenosis, and none of them were noted to have experienced visual disturbances at FU.

Cases of branch vessel occlusion have been reported, indicating that if the opening of such a vessel is covered by a PED, it can become occluded under some conditions, presumably via interference with 'pressure gradient' dependent blood flow. According to these case reports, multiple coaxial PED constructs seem to be associated with an increased risk of branch vessels occlusion. Probably this could be due to an increased surface area being covered and occluding branch vessels openings, resulting in a reduced blood flow and from insufficient patency. Conditions associated with an increased risk of branch vessel occlusion are yet to be studied.

Single stent versus double stents

The design of the PED allows coaxial overlapping in order to increase the degree of aneurysm coverage. There were six aneurysms (Table 1) in our series embolised by two overlapping PEDs; four were large (>10 mm) and two were residual. Regarding three out of the six aneurysms that were treated with overlapping PEDs, all showed complete occlusion, while six out of the seven aneurysms treated with a single PED showed complete occlusion. We tended to treat larger aneurysms with composite constructs to provide a larger area of coverage. As the nature of lesions treated by single and overlapping PEDs was quite different, and the number of lesions was small, further study is required before formulating conclusions about the comparative effectiveness of single PEDs versus multiple overlapping PEDs.

In our department, there was no strict criterion for selecting composite constructs. Their deployment depended on the chief neurosurgeon or interventional radiologist's preference. The technique used for composite constructs was to deploy a longer, larger calibre PED across the aneurysm neck to start with, then, a shorter, smaller calibre PED was telescoped through the established lumen. To further increase the surface coverage across the aneurysm neck, in some cases we deliberately compressed the inner PED longitudinally along the direction of parent vessel. The aim of composite PED constructs is to increase the surface coverage, particularly across the aneurysm neck while leaving vessel segment beyond aneurysm neck covered by a single layer of PED. No more than two overlapping PEDs were used in such constructs.

The Budapest experience,[6] published in February 2010, reported the use of multiple coaxial PEDs. In their series, branches that manifested delayed occlusion were covered by two to four overlapping devices. A single-layer PED did not cause any thrombosis of side branches.

We contend that the surface area coverage resulting from composite PED constructs is difficult to be predicted. First, the pattern of how the microfilaments of two overlapping PEDs are arranged cannot be manipulated. Second, the PED can become compressed to a variable length when being deployed. These cause a variable degree of distortion, and the resultant surface area coverage is also variable. Whether or not a composite PED construct can result in a significantly improved likelihood of complete aneurysm occlusion remains uncertain, and there is no clinical evidence to suggest what percentage of surface coverage should be regarded safe for maintaining branch vessel patency. In considering composite PED construct, caution is therefore necessary, especially if eloquent branch vessel coverage is unavoidable.

In-stent thrombosis/stenosis

Cases of in-stent thrombosis or stenosis have been reported in the literature. A few were associated with antiplatelet agents not being taken properly, as reported by Szikora et al[6] in the Budapest experience.

A case of delayed thrombosis resulting in complete occlusion of the parent vessel 23 months after PED reconstruction was reported by Fiorella et al.[9] In that case, complete occlusion of the aneurysm was confirmed by angiography after 1 year. The aetiology of such very late thrombosis following a PED construct remains unknown.

The Buenos Aires experience[3] reported three (8%) patients with mild (25-50%) in-stent stenosis, two (5%) with moderate (50-70%) in-stent stenosis, and two (5%) with severe (>70%) in-stent stenosis, out of 38 vessels having 3-month angiographic FU. Three of these cases resolved to some extent by the 6-month FU angiogram; one mild case had resolved completely. All of these patients were asymptomatic and none were treated. The PITA trial[5] reported one (3%) of the patients with mild (25-50%) in-stent stenosis, and none with greater in-stent stenosis.

In our series, out of the 10 parent vessels treated by PED embolisation, no in-stent parent vessel occlusion was noted; one patient (No. 7) had a clinically silent in-stent stenosis (approximately 40%) revealed at his 3- and 12-month FU DSA.

These cases of in-stent thrombosis or stenosis reflect the importance of antiplatelet medication to avoid thromboembolic complications after PED reconstruction. As the PED is an investigational device, the proper antiplatelet regimen, especially for local Chinese patients, still warrants further study.

Based on the assumption that Chinese patients have a relatively lower thromboembolic risk compared to others, our department adopted an antiplatelet regimen involving clopidogrel (75 mg daily) for all patients, and additional aspirin (80 mg daily) on a case-by-case basis. This differed from the double antiplatelet regimen reported in other published series.[3,6] Comparing the in-stent stenosis rates of 10% in our series to that in the Buenos Aires experience[3] (18%), the antiplatelet regimen we adopted for PED reconstructions seemed satisfactory for Chinese patients, as long as they have maintained good compliance for at least 6 months.

Stent migration

One patient (No. 1) in our series had stent migration distally, after an overlapping PED construct (3.25 x 20 mm and 3 x 12 mm) was deployed across a previously coiled residual aneurysm with an aneurysmal neck of 10 mm. The immediate post-procedure DSA showed satisfactory contrast stasis. However, distal migration of the PED was noted in the subsequent FU DSA. The residual neck showed a slight decrease in size in serial FU DSAs. Further coil embolisation was not possible for the residual aneurysm as the micro-catheter could not be passed through the PED lumen. Another PED deployment across the aneurysm's neck was a treatment option if the residual neck persists at subsequent FU.

Conclusions

To date, the clinical results of using the PED appeared encouraging for the treatment of non-ruptured internal carotid artery aneurysms. However, larger studies with longer FU duration are warranted, so that complications and durability of PED constructs for internal carotid artery aneurysms can be properly assessed.

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