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ORIGINAL  
RESEARCH

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# Efficacy and Safety of Flow Diversion for Paraclinoid Aneurysms: A Matched-Pair Analysis Compared with Standard Endovascular Approaches

**BACKGROUND AND PURPOSE:** Flow diversion is a new strategy for the treatment of complex paraclinoid aneurysms. However, flow diverters have, to date, not been tested in direct comparison with other available treatments. We present a matched-pair comparison of paraclinoid aneurysms treated with the PED versus other endovascular techniques.

**MATERIALS AND METHODS:** Twenty-one eligible patients with 22 paraclinoid aneurysms treated with the PED at our institution were matched with historic controls with aneurysms of similar size and location.

**RESULTS:** There were no statistically significant differences between the 2 groups in terms of aneurysm size, location, risk factors, or comorbidities. Mean dome size was  $13.9 \pm 6.7$  mm in the control group and  $14.9 \pm 6.3$  mm in the PED group ( $P = .52$ ). Balloon and stent assistance were used in 31.8% and 9.1% of controls, respectively, while carotid sacrifice was used in 36.4% of the controls. There was a significant difference in the rate of complete occlusion favoring PED at radiologic follow-up ( $P = .03$ ).

**CONCLUSIONS:** Flow diverters achieve a much higher rate of complete angiographic obliteration compared with other standard endovascular techniques in the treatment of internal carotid artery aneurysms. In this series, this higher angiographic obliteration rate did not occur at the expense of an increased rate of complications. Careful long-term follow-up is of the utmost importance to definitively validate flow diversion as a superior therapeutic strategy for proximal internal carotid artery aneurysms.

**ABBREVIATIONS:** PED = Pipeline Embolization Device; PUFS = Pipeline Embolization Device for Uncoilable or Failed Aneurysms

Flow diversion has been proposed as a new strategy in the treatment of complex intracranial aneurysms.<sup>1,2</sup> In April 2011, the FDA approved the PED (Chestnut Medical Technologies, Menlo Park, California) for treatment of large wide-neck aneurysms arising from the ICA proximally to the takeoff of the posterior communicating artery. Several single-center series<sup>3-6</sup> and a few multicenter retrospective and prospective studies have demonstrated the efficacy and relative safety of these devices.<sup>7-11</sup> However, flow diverters have not, to date, been tested in direct comparison with other available treatments. In the current study, we conducted a retrospective matched-pair comparison of paraclinoid aneurysms treated with the PED versus other endovascular techniques.

## Materials and Methods

The study was approved by the local institutional review board. The Pipeline Embolization Device was available at our institution as of June 2009, and since then, we have maintained a prospective data base with information regarding patient age, symptomatic status, location and size of the aneurysm, number of devices used, length of hospital stay, and early and late technical and clinical complications. Every

patient had a scheduled follow-up angiogram at least 6 months following treatment. Patients were excluded from this study if the aneurysm was localized in segments other than the ICA proximal to the takeoff of the posterior communicating artery or if the patients had not yet reached a 6-month follow-up point. Every eligible patient treated with the PED was matched to a historic control patient with an aneurysm of similar size and location as well as with a similar history of previous or no previous treatment of the aneurysm (surgical or endovascular).

Given the relatively small number of patients who fulfilled the criteria set up for the study, we did not incur in any situation in which >1 match was available for a given patient treated with the PED. Information regarding control aneurysms was obtained from our data base of aneurysms treated with endovascular techniques since 1999.

Index cases and controls were also matched for the length of radiologic follow-up, though in the control group, radiologic follow-up included either DSA or MRA. Location of the index aneurysm was classified according to the classification proposed by Bouthillier et al.<sup>12</sup> Aneurysm occlusion was graded by using the 3-point modified Raymond scale.<sup>13</sup> Continuous data are presented as mean  $\pm$  SD. Categorical data were compared with the  $\chi^2$  or Fisher exact test. The Wilcoxon rank sum test and the Student *t* test were used to compare continuous data between 2-level categorical variables. Univariate logistic regression models were assessed, and odds ratios (95% confidence intervals) are reported. Results were considered significant for *P* values  $\leq .05$ . All statistical analyses were performed with JMP software, Version 9.0.1 (SAS Institute, Cary, North Carolina).

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**Table 1: Demographic features of patients**

	Control (n = 21)	PED (n = 21)	P Value
Age (mean) (yr)	58.3 ± 18.6	51.0 ± 12.8	.15
Female	19 (90.5%)	18 (85.7%)	.63
Hypertension	13 (61.9%)	9 (42.9%)	.22
Diabetes mellitus	1 (4.8%)	1 (4.8%)	1.00
Previous SAH	0	2 (9.5%)	.15
Family history of intracranial aneurysm	2 (9.5%)	1 (4.8%)	.55
Tobacco			.11
Current	2 (9.5%)	7 (33.3%)	
Prior (<1 yr)	4 (19.1%)	5 (23.8%)	
No	15 (71.4%)	9 (42.9%)	

**Table 2: Main features of aneurysms**

	Control (n = 22)	PED (n = 22)	Total	P Value
Dome size				
Mean (mm)	(13.9 ± 6.7)	(14.9 ± 6.3)		.52
Range (mm)	4–30	6–26		
Median (mm)	13	14.5		
Small	7 (31.8%)	7 (31.8%)	14 (31.8%)	
Large	12 (54.5%)	12 (54.5%)	24 (54.5%)	
Giant	3 (13.6%)	3 (13.6%)	6 (13.6%)	
Location				
Carotido-ophthalmic	12 (54.5%)	12 (54.5%)	24 (54.5%)	
Cavernous	9 (40.9%)	9 (40.9%)	18 (40.9%)	
Hypophyseal	1 (4.5%)	1 (4.5%)	2 (4.5%)	

**Table 3: Treatment modality**

	Control	PED
Only coils	14 (63.6%)	0
Balloon-assisted	7 (31.8%)	0
Stent-assisted	2 (9.1%)	0
Iatrogenic occlusion	8 (36.4%)	0

## Results

Twenty-one patients were treated with the PED. Among these, all patients had available 6-month follow-up angiography and 13 patients had available 12-month angiography. Basic demographic characteristics and risk factors between the 2 groups are summarized in Table 1. There were no statistically significant differences between the 2 groups in terms of aneurysm size, location, risk factors, and comorbidities, though there was a trend for patients in the control group to be older and, as a consequence, to have a higher incidence of hypertension. In each group, there were 3 (13.6%) giant aneurysms ( $\geq 25$  mm), 12 (54.5%) large (11–24 mm), and 7 (31.8%) small aneurysms. All the aneurysms treated had a wide neck ( $>4$  mm). Carotido-ophthalmic aneurysms were the most common (54.5%), followed by intracavernous aneurysms (40.9%) and superior hypophyseal aneurysms (4.5%). Mean dome size was  $13.9 \pm 6.7$  mm in the control group and  $14.9 \pm 6.3$  mm in the PED group ( $P = .52$ ). Characteristics of aneurysms are summarized in Table 2. Balloon and stent assistance were used in 31.8% and 9.1% of controls, respectively, while carotid sacrifice was used in 36.4% of the controls (Table 3).

The mean length of stay was not significantly different between the 2 groups ( $2.2 \pm 1.9$  days for control group and  $1.6 \pm 0.9$  days in the PED group,  $P = .41$ ). Technical and access periprocedural complications are listed in Table 4. Periproce-

**Table 4: Clinical and technical complications**

	Control (n = 4)	PED (n = 3)	P Value
Complications			
Periprocedural technical			1.00
Perforation	1 (4.5%)	0	
Coil-prolapsing flow-limiting	1 (4.5%)	0	
Thrombus formation	2 (9.1%) <sup>a</sup>	1 (4.5%)	
Catheter-induced vasospasm	0	1 (4.5%)	
In-stent stenosis (balloon use)	0	1 (4.5%)	1.00
Early clinical (No.)	3	2	
GI bleed	0	1 (4.5%)	
Hemodynamic instability	1 (4.5%)	0	
Transient right weakness (no stroke)	1 (4.5%)	0	
Groin hematoma	0	1 (4.5%)	
Transient worsening of ophthalmoparesis	0	1 (4.5%)	
Retroperitoneal hematoma	1 (4.5%)	0	

**Note:**—GI indicates gastrointestinal.

<sup>a</sup> Intraoperative thrombolytic use.

**Table 5: Degree of obliteration at radiologic follow-up**

	Control	PED	Odds Ratio (95% CI)	P Value
Class 1	10 (45.4%)	17 (77.3%)	4.1 (1.1–15.1)	.03
Class 2	7 (31.8%)	3 (13.6%)		.22
Class 3	5 (22.7%)	2 (9.1%)		.15

**Note:**—CI indicates confidence interval.

**Table 6: Degree of occlusion<sup>a</sup>**

	Control (14 Aneurysms)	PED (21 Aneurysms)	Odds Ratio (95% CI)	P Value
Class 1	3 (21.4%)	16 (76.2%)	11.7 (2.3–5)	.0014
Class 2	7 (50.0%)	3 (14.3%)	0.2 (0.03–0.83)	.02
Class 3	4 (28.6%)	2 (9.5%)		.14

**Note:**—CI indicates confidence interval.

<sup>a</sup> After excluding the 8 patients treated with parent artery sacrifice in the control group and the patient found to have an asymptomatic ICA occlusion in the PED group.

dural clinical complications in the PED group included gastrointestinal bleed for 1 patient (4.5%) and transient worsening of ophthalmoparesis (4.5%) and a groin hematoma that required surgical repair for another one (4.5%), while the control group included transient right weakness of upper and lower extremities (4.5%, solved spontaneously, without evidence of stroke) and hemodynamic instability (4.5%, for a patient who had a retroperitoneal hematoma).

There was a significant difference in the rate of complete occlusion favoring PED at radiologic follow-up ( $P = .03$ ) (Table 5). One patient in the PED group was found to have an asymptomatic ICA occlusion diagnosed at a routine 6-month follow-up study. No stenosis within the device was observed in any of the patients treated with PED. Late clinical complications included 1 patient who started having episodes consistent with amaurosis fugax 22 months after treatment with the PED. These resolved after reinstitution of antiplatelet therapy.

After excluding the 8 patients who underwent carotid sacrifice and the patient treated with PED who was found to have an asymptomatic carotid occlusion, 21.4% of controls versus 76.2% of patients treated with PED were found to have complete aneurysm exclusion ( $P = .0014$ ) (Table 6). In the control group, patients treated with arterial preservation were treated with coils alone (7 patients, 50.0%), balloon-assisted coiling (5 patients, 35.7%), and stent-assisted coiling (2 patients,

14.3%). Carotid sacrifice in the control group was achieved by using coils in 6 patients and balloons in the remaining 2.

## Discussion

In this retrospective matched-pair analysis, we found a significantly higher incidence of complete occlusion at follow-up in patients treated with the PED compared with similar aneurysms matched for size and location that were treated with other “conventional” endovascular techniques. In the PED group, by using very strict angiographic criteria, complete occlusion on DSA was achieved in three-quarters of patients, while such occlusion was achieved in less than one-half of patients treated by conventional means. Notably, rates of adverse events were similar between groups. These results suggest strongly that flow diversion might improve long-term angiographic outcomes in patients with “difficult” aneurysms in the periorbital region and may offer substantial benefit over other endovascular options.

The incomplete degree of angiographic obliteration and the risk of aneurysm recurrence have been the main limitations of endovascular treatment of intracranial aneurysms. These limitations have been the impetus behind the modifications of the coil (such as bioactive coils, coating with expandable materials like hydrogel, and so forth) and the development of microcatheter-delivered stents to be used in stent-assisted coiling procedures. Despite these advances, the recurrence rate and the rate of incomplete angiographic obliteration after aneurysm treatment with “modified” or “biologically” active coils and stent-assisted coiling continue to be discouragingly high.<sup>14,15</sup> Flow diverters may fill the need for a more effective and definitive endovascular treatment, especially as it applies to paraclinoid aneurysms. Flow diverters seem to have multiple theoretic and some demonstrated properties that may increase the degree of angiographic obliteration and, with time, promote aneurysm shrinkage.<sup>16,17</sup> By redirecting flow into the parent artery and away from the aneurysm sac, flow diverters induce progressive aneurysm thrombosis leading to angiographic obliteration with time. As the clot organizes and retracts, aneurysm shrinkage ensues.<sup>18–21</sup> Moreover, the presence of the flow diverters in the aneurysm neck provides structural support of the “diseased” portion of the vessel, and with time as the device is incorporated into the vessel wall, it is covered by an endothelial layer that “seals” the neck.<sup>22,23</sup>

The high rate of complete angiographic occlusion at follow-up that we have observed is in line with that in other studies, though other studies did not have a control group. The PUFs study is the study that eventually led to FDA approval of the PED.<sup>10</sup> In this multicenter prospective study, only giant and large aneurysms of the proximal ICA with wide necks were included. In PUFs, the rate of complete angiographic obliteration was 82% at 6 months and 86% at 1 year (T. Bekske for the PUFs investigators, presented in Colorado Springs, July 2011, unpublished data). Lylyk et al,<sup>5</sup> in a large single-center consecutive series of 54 patients, reported rates of complete angiographic obliteration of 56%, 93%, and 95% of aneurysms at 3, 6, and 12 months, respectively. Our data are similar to those in these prior reports, with high rates of complete occlusion; we have added important additional information in that we included similar types and sizes of aneurysm

treated by other endovascular means so that practitioners can better assess the relative merits of flow diversion compared with coil embolization or parent artery sacrifice.

Treatment with flow diverters is particularly effective in aneurysms involving the proximal internal carotid artery. These aneurysms have a “sidewall” geometry, which makes them more suitable for these treatment paradigms. Proximal ICA aneurysms often have a fusiform shape with involvement of the entire circumference of the vessel, which makes them less suitable for effective treatment with other conventional endovascular techniques. In our study, 36.4% of the controls had been treated with parent artery sacrifice. While parent artery sacrifice is a well-established and effective treatment technique for aneurysms of the proximal internal carotid artery, several limitations of this approach exist. These are related to the risk of flow-related aneurysm formation along the collateral pathways and to the decrease in cerebrovascular reserve after 1 carotid artery has been sacrificed. Moreover, because proximal carotid aneurysms are often related to an “intrinsic” weakness of the vessel wall in this segment, patients with these aneurysms often have contralateral aneurysms or are at high risk of developing contralateral mirror aneurysms, which makes carotid artery sacrifice a less appealing option.

The effectiveness of flow diverters has to be weighed against their safety. In our study, complications with flow diverters were not significantly different from those in controls, and in the PED group, no patient had a permanent neurologic deterioration. Other studies have also confirmed the relative safety of these devices, despite the complexity of aneurysms treated. In the PUFs study, the rate of major ipsilateral stroke or neurologic death was 5.6%, while the intracranial hemorrhage rate was 4.7%.<sup>10</sup> Midterm safety is also confirmed by our and other studies.<sup>3,5,8,9</sup> We did not observe new permanent neurologic deficits after a mean follow-up of  $13.4 \pm 6.9$  months, and only 1 patient had episodes possibly consistent with amaurosis fugax 22 months after treatment. These episodes resolved after reinstitution of antiplatelet therapy. The durability of the device is also confirmed in our study because only 1 patient had an asymptomatic internal carotid artery occlusion and no hemodynamically significant ( $>50\%$ ) stenosis was observed at 6 months in any of the patients or at 12 months in 13 patients who reached this follow-up milestone. In the PUFs study, stenosis of  $>50\%$  occurred in 2 patients (1.9%) and 1 patient (1%) was found to have an asymptomatic ICA occlusion at the 6-month follow-up. Delayed aneurysm rupture (usually within the first 2 weeks of treatment) and distal hemorrhages have been reported after treatment with flow diverters and are one of the major concerns of this technology. No such events were observed in this series, and the causes leading to these feared and often devastating complications are still mostly unknown.

Our study has limitations. While the data for patients in the PED group were collected prospectively, data for the controls were retrospectively collected. Moreover, patients in the PED group were treated during the past 2 years, while controls had been treated across a longer and earlier interval and increased experience may have accounted for some of the better results seen with the PED. However, this effect would have been partially counteracted by the steep learning curve for the PED. While every patient in the PED group had at least 1 control

DSA at follow-up, radiologic follow-up consisted of MRA in 14 (66.7%) patients in the control group, but this, if anything, should skew the results against the PED because MRA is not as sensitive as DSA in depicting persistent flow within the aneurysm. These limitations notwithstanding, our study is the only study comparing results of flow diversion with results of treating similar aneurysms with other endovascular techniques, to our knowledge.

## Conclusions

Flow diverters achieve a much higher rate of complete angiographic obliteration compared with other standard endovascular techniques in the treatment of internal carotid artery aneurysms. In this series, this higher angiographic obliteration rate did not occur at the expense of an increased rate of complications. Flow diversion has largely supplanted advanced endovascular techniques such as balloon-assisted and stent-assisted coiling and has decreased significantly the need for parent artery sacrifice in the treatment of complex internal carotid artery aneurysms. Careful long-term follow-up is of utmost importance to definitively validate flow diversion as a superior therapeutic strategy for proximal internal carotid artery aneurysms.

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