A Single Pipeline Embolization Device is Sufficient for Treatment of Intracranial Aneurysms

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ABSTRACT

BACKGROUND AND PURPOSE: The Pipeline Embolization Device has emerged as an important treatment option for intracranial aneurysms. The number of devices needed to treat an aneurysm is uncertain and is the subject of vigorous debate. The purpose of this study was to compare rates of complications, aneurysm occlusion, and outcome in patients treated with a single-versus-multiple Pipeline Embolization Devices.

MATERIAL AND METHODS: One hundred seventy-eight patients were treated with the Pipeline Embolization Device at our institution. Patients were divided into 2 groups: a single-device group ($n = 126$) and a multiple-device group ($n = 52$).

RESULTS: There was no statistically significant difference between the 2 groups with respect to baseline characteristics except for age and aneurysm size (higher with multiple Pipeline Embolization Devices). Complications occurred more frequently with multiple (15%) versus a single device (5%, $P = .03$). In multivariate analysis, the use of multiple devices independently predicted complications. A similar proportion of patients achieved adequate aneurysm obliteration at follow-up in the single-device (84%) and the multiple-device groups (87%, $P = .8$). In multivariate analysis, age and follow-up time predicted obliteration. At follow-up, a significantly higher proportion of patients treated with a single device (97%) achieved a favorable outcome compared with those treated with multiple devices (89%, $P = .03$). In multivariate analysis, there was a strong trend for the use of a single device to predict favorable outcomes ($P = .06$).

CONCLUSIONS: Treatment with a single Pipeline Embolization Device provides similar occlusion rates with less complications and better overall outcomes. These findings suggest that a single Pipeline Embolization Device is sufficient for treatment of most intracranial aneurysms.

ABBREVIATIONS: ICH = intracerebral hemorrhage; PED = Pipeline Embolization Device

The Pipeline Embolization Device (PED; Covidien, Irvine, California) is a dedicated flow diverter, which received US Food and Drug Administration approval in 2011 for the treatment of large and giant wide-neck aneurysms of the internal carotid artery. The device appears to be highly efficient in promoting durable aneurysm occlusion, and its safety profile has been shown to be favorable in several well-designed studies.[1-3] In an increasing number of cerebrovascular centers, the PED has become a routine first-line option for unruptured intracranial aneurysms.

The number of PEDs needed to treat an aneurysm is uncertain and is the subject of vigorous debate at present.[4] The question is a crucial one and has potential implications for procedural cost, safety, and efficacy. To our knowledge, this is the first study to compare rates of complications, aneurysm occlusion, and outcome in patients treated with single-versus-multiple PEDs.

MATERIALS AND METHODS
Patient Population

The study protocol was approved by the Thomas Jefferson University Institutional Review Board. All patients with intracranial aneurysms treated with the PED at our institution between May 2011 and May 2013 were identified from a prospectively maintained data base. One hundred seventy-eight patients were treated during this period and constituted our study population.

The patient population was divided into 2 groups based on the number of PEDs deployed during initial aneurysm embolization. There were 126 (70.8%) patients treated with a single device and 52 (29.2%) patients treated with >1 device. The rates of compli-

cations, aneurysm obliteration, retreatment, and clinical outcome were compared between the 2 groups. All symptomatic procedural complications were included. Delayed complications were also recorded through follow-up. Angiographic follow-up was scheduled at 3–6 months, 1 year, 2 years, and 5 years after treatment. Aneurysm occlusion at follow-up was categorized as complete/near-complete (≥90%) or incomplete (<90%). Clinical follow-up was performed at 1, 3, and 6 months. Outcome was reported according to the modified Rankin Scale.

Technique

All patients received 75 mg/day of clopidogrel (Plavix) and 81 mg/day of aspirin for 10 days before the procedure. Platelet function tests were performed on all patients by using aspirin and P2Y12 assays (VerifyNow; Accumetrics, San Diego, California). The procedure was performed only if the platelet inhibition level was >30% but less <90%. Patients with inhibition <30% were reloaded, and the assay was rechecked. Patients found to be poor responders to clopidogrel were then switched to prasugrel (40-mg loading dose followed by a 5-mg daily maintenance dose). Patients with inhibition above 90% were admitted to the hospital, their procedure was canceled, and clopidogrel was held until the platelet inhibition level fell below 90%. An initial heparin bolus was administered, and activated clotting time was maintained at 2–3 times the patient's baseline intraoperatively. Heparin was discontinued at the end of the procedure. Patients were maintained on dual antiplatelet therapy for at least 6 months after the procedure followed by aspirin indefinitely.

PEDs were generally deployed through a Marksman microcatheter (Covidien) by using a triaxial guide-catheter system to maximize support during forward loading of the system and to optimize stent opening and apposition. Inadequate vessel wall apposition was remedied with balloon angioplasty when needed. The number of devices deployed was dependent on the operator's preference and experience but was also based on subjective assessment of intra-aneurysmal stasis. When the landing zone was missed, further devices were placed to cover the aneurysm neck. In addition, we may tend to use >1 device specifically for fusiform aneurysms. In the basilar artery, whenever possible, we try to avoid using >1 device to preserve the patency of side branches. Placement of additional PEDs was considered at follow-up if the aneurysm remained unchanged or did not sufficiently decrease in size despite treatment.

Statistical Analysis

Data are presented as mean and range for continuous variables and as frequency for categoric variables. Analysis was performed by using an unpaired t test, Wilcoxon rank sum test, χ^2 test, and Fisher exact test as appropriate. Univariate analysis was used to test covariates predictive of the following dependent variables, each independently: complications, aneurysm obliteration at follow up, retreatment, and unfavorable outcome (mRS 3–6). Interaction and confounding were assessed through stratification and relevant expansion covariates. Factors predictive in univariate analysis ($P < .20$)[5] were entered into a multivariate logistic regression analysis. P values ≤.05 were considered statistically signifi-

Table 1: Aneurysm locations

Aneurysm Location	1 PED (%)	Multiple PEDs (%)
Carotid cavernous artery	17 (13.5)	13 (25)
Carotid ophthalmic artery	53 (42)	19 (36.5)
Paraclinoid artery	36 (28.6)	7 (13.5)
Middle cerebral artery	4 (3.1)	5 (9.6)
Basilar trunk	3 (2.4)	2 (3.8)
Posterior circulation (other than basilar trunk)	8 (6.4)	4 (7.7)
Other	5 (4.0)	2 (3.9)
Total	126	52

cant. Statistical analysis performed with STATA 10.0 (StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics

The proportion of female patients was 86% (108/126) in the single-PED group and 81% (42/52) in the multiple-PED group ($P = .4$). Patients in the multiple-PED group were significantly older than those in the single-PED group (mean age, 61.1 years versus 54.2 years; $P = .002$). Mean aneurysm size was also higher in the multiple-PED group (11.8 mm versus 9.2 mm, $P = .02$), but the proportion of patients with large aneurysms did not differ significantly between the 2 groups (39%, 49/126, with a single PED versus 52%, 27/52, with multiple PEDs; $P = .2$). The proportion of aneurysms arising from the posterior circulation did not differ between the 2 groups (8.7%, 11/126, with a single PED versus 11.5%, 6/52, with multiple PEDs; $P = .6$). Likewise, the proportion of aneurysms arising from the basilar trunk did not differ between the 2 groups (2.4%, 3/126, with a single PED versus 3.8%, 2/52, with multiple PEDs; $P = .8$). The distribution of aneurysm locations is detailed in Table 1. Fusiform or dissecting aneurysms accounted for 12.7% (16/126) and 23% (12/52) of aneurysms treated with a single and multiple PEDs, respectively ($P = .09$). The proportion of previously treated aneurysms was comparable in those treated with single (20.6%, 26/126) versus multiple devices (19.2%, 10/52; $P = .8$).

Adjunctive coiling was undertaken in 11% (14/126) of aneurysms treated with a single PED versus 5.8% (3/52) of those treated with multiple PEDs ($P = .3$). Balloon angioplasty was necessary in ≈9.5% (12/126, 5/52) of patients in either group ($P = .9$). A single PED was used in 126 (70.8%) patients; 2 PEDs, in 40 (22.5%); 3 PEDs, in 7 (3.9%); 4 PEDs, in 4 (2.3%); and 5 PEDs, in 1 (0.7%).

Outcomes

Complications occurred more frequently in those treated with multiple (15%, 8/52) versus a single device (5%, 7/126, $P = .03$). In the single-device group, there were 3 hemorrhagic complications (1 distal parenchymal hemorrhage, 1 spontaneous delayed aneurysm rupture after 4 months, and 1 aneurysm rupture due to proximal device migration causing a direct jet of blood against the dome) and 4 ischemic complications (1 associated with distal device migration in a patient with schizophrenia who was not compliant with his antiplatelet regimen). In the multiple-PED group, there were 4 hemorrhagic complications (all distal parenchymal

Table 2: Aneurysm obliteration

Latest Occlusion	Single PED (%)	Multiple PED (%)	Total (%)
Complete (100%)	58 (68.2)	28 (70)	86 (68.8)
Near-complete (90%–99%)	13 (15.3)	7 (17.5)	20 (16)
Incomplete (<90%)	15 (16.5)	5 (12.5)	19 (15.2)
Total	85	40	125

hemorrhages) and 4 ischemic complications. None of the hemorrhagic complications occurred in patients with middle cerebral artery aneurysms. The following factors were tested as predictors of complications: age, sex, aneurysm location, aneurysm size, aneurysm morphology, previous aneurysm treatment, number of PEDs used per aneurysm, adjunctive use of coils, and balloon angioplasty. In univariate analysis, predictors of complications were the following: 1) increasing age ($P = .04$); 2) increasing aneurysm size ($P = .004$); and 3) the use of >1 device ($P = .04$). These factors were subsequently entered into a multivariate analysis. In multivariate analysis, the use of >1 device was the only statistically significant predictor of complications (OR = 3.0; 95% CI, 1.1–8.8; $P = .04$).

Angiographic follow-up was available for 85 patients in the single-PED group and 40 patients in the multiple-PED group. Mean follow-up time was longer in the multiple- (8.9 months) than in the single-PED group (7.0 months, $P = .01$). A similar proportion of patients achieved complete or near-complete aneurysm obliteration at follow-up in the single-device (71/85, 84%) and multiple-device (35/40, 87%, $P = .8$) groups (Table 2). The following factors were tested as predictors of aneurysm obliteration: age, sex, aneurysm location, aneurysm size, aneurysm morphology, previous aneurysm treatment, number of PEDs used per aneurysm, adjunctive use of coils, balloon angioplasty, procedural complications, and angiographic follow-up time. In univariate analysis, the following factors were negative predictors of aneurysm obliteration (<90%): 1) increasing age ($P = .1$), and 2) decreasing angiographic follow-up duration ($P = .09$). In multivariate analysis, increasing age (OR = 0.4; 95% CI, 0.16–0.91; $P = .03$) and decreasing angiographic follow-up duration (OR = 0.9; 95% CI, 0.8–0.99; $P = .04$) were independent negative predictors of aneurysm obliteration. The number of devices was not a predictive factor, even after controlling for these variables.

Retreatment was necessary in a similar proportion of patients after embolization with single (6%, 5/85) or multiple devices (7.5%, 3/40, $P = .8$). In-stent stenosis was noted in ≈5% (4/85, 2/40) of patients in each group ($P = .95$).

Clinical follow-up was available for 125 patients in the single-PED group and 52 patients in the multiple-PED group. At the latest follow-up, a significantly higher proportion of patients treated with a single device (97%, 121/125) achieved a favorable outcome (mRS 0–2) compared with those treated with >1 device (89%, 46/52, $P = .03$). In the single-PED group, 3 of the 4 patients with an unfavorable outcome sustained a procedural complication and 1 was disabled at baseline. In the multiple-PED group, 4 of the 6 patients with an unfavorable outcome sustained a complication and 1 was severely disabled before PED treatment. The same factors as those used for occlusion were tested as predictors of clinical outcome. In univariate analysis, the following factors

were predictors of unfavorable outcome (mRS > 2): 1) increasing aneurysm size ($P > .001$), and 2) the use >1 device ($P = .03$). In multivariate analysis, increasing aneurysm size (OR = 1.1; 95% CI, 1.06–1.6; $P = .001$) was an independent predictive factor, and there was a strong trend toward the use of >1 device to predict unfavorable outcome (OR = 3.5; 95% CI, 0.9–13; $P = .06$).

DISCUSSION

Flow diversion is now a well-established treatment for intracranial aneurysms.[2,6-10] Flow diverters, most typically the PED, have proved to be more efficient than and at least as safe as traditional embolization strategies.[6,11,12] Lanzino et al[13] reported a significantly higher rate of complete occlusion in patients with the PED (76%) than in patients (21%) treated with coils with a similar rate of morbidity. Likewise, Chalouhi et al[2] compared the safety and efficacy of the 2 techniques in unruptured, large, and giant (≥10 mm) aneurysms, reporting a similar complication rate (7.5%) and a higher aneurysm occlusion rate (86% versus 41%) with flow diversion. They concluded that the PED is a preferred treatment option for large unruptured saccular aneurysms. The Pipeline for Uncoilable or Failed Aneurysms study is a recently published prospective, international multicenter series that included large and giant, wide-neck aneurysms arising from the internal carotid artery.[1] The results of this study confirmed the safety (5.6% rate of major ipsilateral stroke or neurologic death) and high efficacy of the PED (73.6% rate of complete occlusion at day 180 without major stenosis of the parent vessel) in the most complex aneurysms.

Aside from thromboembolic complications, which may occur in any neuroendovascular procedure, treatment with flow diverters carries the risk of specific complications not encountered with standard embolization techniques. Distal intracerebral hemorrhage (ICH) is a dreaded complication of flow diversion, and its incidence is reported to be approximately 1%–2%.[14,15] The mechanism of ICH after flow diversion may involve hemorrhagic conversion of ischemic infarcts in the setting of dual antiplatelet therapy, modification of intracranial blood pressure in the distal territories, and intraprocedural embolization of foreign material.[2,16,17] Delayed aneurysm rupture after flow diversion occurs in approximately 1.0% of patients, and its mechanism may involve sudden hemodynamic changes in intra-aneurysmal flow patterns or aneurysm wall weakening due to inflammation and proteolytic enzymes within the developing red thrombus.[17] Some have suggested using intraluminal coils or steroids to attenuate the effects of intra-aneurysmal thrombosis, but whether this strategy can reduce the risk of aneurysm rupture remains to be seen. Last, device migration has recently been recognized as a potential, severe complication of flow diversion that can be associated with hemorrhagic or thromboembolic events.[18] Migration may occur proximally or distally and is related to the mismatch in arterial diameter between inflow and outflow vessels and to stretching of the device.[19]

The present study was undertaken to address a pressing and crucial question that has been recently debated in the neurointerventional community. Specifically, we aimed to determine whether treatment with a single PED is sufficient for treatment of intracranial aneurysms. Although there might not be a categoric

answer to this question, this study provides strong evidence supporting the use of only a single PED in the initial treatment of aneurysms. As such, the complication rate was thrice as high in the multiple-device group (15%) compared with the single-device group (5%). Moreover, the use of >1 device was a strong independent predictor of complications with an odds ratio as high as 3. We believe that this is explained by a higher propensity for thromboembolic complications with the use of multiple PEDs, which are highly thrombogenic constructs with high metal surface area coverage. Because ICH may be secondary to ischemic lesions, hemorrhagic events are more likely to occur when multiple devices are used as well. In addition, it is well known that placement of the second and third PED is usually more technically complex, given the presence of the previously deployed device. The difficulty of deploying PEDs over previous stents has been highlighted in a recent article.[10] Although one may naturally tend to think that placing additional devices provides further flow diversion and better angiographic results, the present study demonstrates similar occlusion rates at follow-up with the use of a single (84%) versus multiple devices (87%). This crucial finding suggests that a single device provides enough flow diversion for occlusion of most aneurysms and that placement of additional devices will only add morbidity, cost, and radiation exposure. Accordingly, we believe that complete intra-aneurysmal stasis during initial embolization is not required for ultimate aneurysm thrombosis and should not be considered the end point of the procedure. Using multiple devices did not decrease the rate of retreatment; this result may suggest that aneurysms that fail flow diversion have an inherent tendency to do so regardless of the number of devices used. The senior author's strategy entails treating most aneurysms with a single PED initially and reserving further device deployment only for those aneurysms that remain unchanged or do not sufficiently decrease in size at the 3- to 6-month follow-up. This strategy avoids the unnecessary use of additional devices and is undoubtedly an important factor in procedural safety. The trend toward better clinical outcomes in the single-device group further supports this strategy. Potential exceptions include fusiform aneurysms, ruptured aneurysms in which immediate occlusion is warranted, and cases in which the initial device has not provided adequate neck coverage or vessel reconstruction. Using multiple PEDs may increase the stability of the construct and prevent device migration.[20] Also, there were no aneurysm ruptures in the multiple-device group. The 2 aneurysm ruptures that occurred in the single-device group may suggest that both could have been prevented with a multiple-device construct from the outset.

Although the studied question has not been previously addressed, the literature may suggest a similar trend. In the German study by Fischer et al,[21] in which multiple devices were used in as many as 66% of cases (median, 3), major complications occurred in 6% of patients. Likewise, the major complication rate was 8.5% in the US multicenter series in which 2.12 PEDs were used on average per aneurysm.[22] In the Canadian experience, O'Kelly et al[23] used >1 device in almost half of the patients and experienced a combined morbidity and mortality rate of 10.7% (6.3% mortality, 4.4% morbidity). In contrast, Lylyk et al[24] used a single PED in 70% of aneurysms and reported a 0% rate of morbidity and mor-

tality. Likewise, Saatci et al[14] used only 1.3 PEDs on average per aneurysm (1 device in ≈70%) and noted a combined morbidity-mortality rate as low as 1.5%. Thus, the use of multiple devices may be associated with higher complication rates and worse clinical outcomes, as corroborated in the present report.

This study is limited by its overall retrospective design, though the safety data on the PED are prospectively recorded at our institution. This study reports the experience of a single cerebrovascular center; thus, results may not be entirely generalizable. Although the 2 groups were well-matched with regard to most baseline characteristics, the older age, larger aneurysm size, and higher proportion of fusiform aneurysms (though not significantly) in the multiple-PED group may have favored the single-device group. Fusiform aneurysms are higher risk lesions with poorer outcomes across all treatment methods. Some may argue that the higher occurrence of intraparenchymal hemorrhages in the multiple-device group may be related to more challenging cases with a higher risk of wire perforations and more manipulation, causing more vessel stretching and tearing. However, in contrast to coiling, complication and recurrence rates with the PED are not affected by aneurysm size.[19,25] This outcome limits the effect of this factor on the comparative analysis. In addition, the shorter follow-up time in the single-PED group has favored the multiple-PED group because the occlusion rate of aneurysms treated with flow diverters increases with time.[3,14] A multivariate analysis was performed to control for those differences, and it identified treatment with multiple devices as an independent predictor of complications and poor outcome (strong trend).

CONCLUSIONS

The results of this study show that treatment with a single PED is associated with fewer complications, better functional outcomes, and similar occlusion rates compared with multiple PEDs. These results suggest that a single PED is sufficient for treatment of most intracranial aneurysms. Placement of additional devices may only add morbidity, cost, and radiation exposure.

In the era of flow diverters, ongoing trials should not only confirm the noninferiority of flow diversion to traditional embolization techniques (which is already known from several well-designed studies) but should also investigate ways to further improve the procedural safety and efficacy of flow diverters.

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