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Multicenter Study of Pipeline Flex for Intracranial Aneurysms

BACKGROUND: The Pipeline Flex (PED Flex; Medtronic, Dublin, Ireland) was designed to facilitate deployment and navigation compared to its previous iteration to reduce the rate of technical events and complications.

OBJECTIVE: To assess the neurological morbidity and mortality rates of the PED Flex at 30 d.

METHODS: Information from 9 neurovascular centers was retrospectively obtained between July 2014 and March 2016. Data included patient/aneurysm characteristics, periprocedural events, clinical, and angiographic outcomes. Multivariate logistic regression was performed to determine predictors of unfavorable clinical outcome (modified Rankin Scale [mRS] > 2).

RESULTS: A total of 205 patients harboring 223 aneurysms were analyzed. The 30-d neurological morbidity and mortality rates were 1.9% (4/205) and 0.5% (1/205), respectively. The rate of intraprocedural events without neurological morbidity was 6.8% (14/205), consisting of intraprocedural ischemic events in 9 patients (4.5%) and hemorrhage in 5 (2.4%). Other technical events included difficulty capturing the delivery wire in 1 case (0.5%) and device migration after deployment in another case (0.5%). Favorable clinical outcome (mRS 0-2) was achieved in 186 patients (94.4%) at discharge and in 140 patients (94.5%) at 30 d. We did not find predictors of clinical outcomes on multivariate analysis.

CONCLUSION: The 30-d rates of neurological morbidity and mortality in this multicenter cohort using the PED Flex for the treatment of intracranial aneurysms were low, 1.9% (4/205) and 0.5% (1/205), respectively. In addition, technical events related to device deployment were also low, most likely due to the latest modifications in the delivery system.

KEY WORDS: Aneurysm, Embolization, Endovascular, Pipeline, Stroke

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Endoluminal reconstruction of intracranial aneurysms with flow diverters has become a widely accepted treatment alternative to coil embolization and microsurgical clipping. Robust evidence from multicenter clinical studies including the PUFS trial,[1] IntrePED,[2] and ASPIRe registries[3] as well as clinical series[4-6] have demonstrated high rates of complete aneurysm occlusion, complication rates comparable to other endovascular treatments, and low rates of aneurysm recurrence. In light of favorable safety profile and effectiveness, the first-generation Pipeline Embolization Device (PED; Medtronic Neurovascular, Medtronic, Dublin, Ireland) received approval from the Conformité Européenne (CE mark) in 2008 and United States FDA in 2011. From a technical standpoint, however, placement of the first-generation PED was challenging compared to self-expandable stents due to the nature of the braided device and delivery system characteristics, resulting in a steep learning curve and procedural complications.[7] In instances of unfavorable deployment or lack of good apposition, several maneuvers were employed such as angioplasty or removal of the device by 'corking' among others.

The second-generation PED, known as Pipeline Flex Embolization Device (PED Flex), was designed to overcome the aforementioned technical problems by replacing the delivery

ABBREVIATIONS: CI, confidence interval; **ICA,** internal carotid artery; **mRS,** modified Rankin Scale; **OR,** odds ratio; **PED,** Pipeline Embolization Device

system and allowing near-complete resheathing prior to deployment. In March 2014, the PED Flex was CE approved for use in Europe and subsequently FDA approved in the United States in February 2015. Since then a few single-center series have been published with encouraging initial results,[8] although a relatively small number of patients have been reported which precludes a definite analysis and comparison with the first-generation PED. The current study was designed to determine the clinical safety of the new PED Flex by identifying potential predictors of clinical outcomes at 30 d and evaluate whether the technical advantages of the PED Flex result in fewer intraprocedural events by analyzing a large population of patients treated in multiple centers with high neuroendovascular volume in the United States.

METHODS

After approval by each local institutional review board, we conducted a retrospective analysis of patients with intracranial aneurysms treated with PED Flex (Medtronic) from July 2014 to March 2016 in 9 centers across the United States. The inclusion criteria consisted of adult patients (≥18 yr old) with unruptured aneurysms located in the anterior or posterior cerebral circulation treated with the PED Flex. Patients with ruptured aneurysms were excluded. None of the patients in the study have been included in previous publications. Written informed consent was not required for this research study due to its retrospective design and a waiver of Health Insurance Portability and Accountability Act privacy authorization was obtained.

Each center collected their own data and reviewed their center's angiographic imaging, which were entered into a standardized data form. Data collected from each patient included demographic information (age and sex), symptoms at presentation, aneurysm characteristics (location, size, and morphology), previous history of index aneurysm treatment, intraprocedural events, number of devices deployed, number of resheathing maneuvers, use of adjunctive coils, periprocedural events (ie, neurological clinical events occurring after the procedure up to 30 d), as well as clinical assessment based on 30-d follow-up and latest clinic visit. Functional outcome was determined based on the modified Rankin Scale (mRS). A fusiform, dissecting or pseudoaneurysm was defined as an aneurysmal dilatation 1.5 times normal diameter without a definable neck involving a portion of an arterial segment with any degree of tortuosity. An irregular aneurysm consisted of a lesion with complex morphology that did not meet saccular or fusiform features. A technical event was defined as either an intraprocedural difficulty to deploy the device or any clinical complication during the intervention. Neurological morbidity was considered when the symptoms after the event (ischemic or hemorrhagic) persisted longer than 7 d. The timing of aneurysm imaging varied across centers although all institutions routinely obtained vascular imaging and assessed aneurysm occlusion. The aneurysm occlusion status was assessed either with cerebral angiogram or Magnetic Resonance Angiography. The degree of aneurysm occlusion was determined according to the scale of Raymond-Roy.[9] The rates of aneurysm retreatment (any intervention at discretion of the neurointerventionalists after the PED Flex placement), in-stent stenosis (≥50%), and device migration were also recorded. Use of PED for aneurysms smaller than 10 mm and outside the petrous internal carotid artery (ICA) to superior hypophyseal segment is considered off-label.

The primary endpoints were to assess the neurological morbidity and mortality rates of the PED Flex at 30 d. Secondary endpoints consisted of intraprocedural technical events, the rates of aneurysm occlusion, in-stent stenosis, retreatment, and the last clinical follow-up available during the study time.

Pipeline Flex

Technical Advantages

The PED Flex device is identical to the first generation of the PED, resulting in the same amount of metal surface area coverage. The delivery wire consists of a 15 mm in length, 0.012″ soft distal tip with a preshaped curve of 55° and a proximal platinum marker for increased visibility. Two 3-mm protective sleeves of nonradiopaque material (polytetrafluoroethylene) protect the distal aspect of the braid and allow increased control during release without the need to maneuver the device into the classic cigar-shape. The proximal aspect of the PED Flex has been placed on a 3-mm resheathing pad that allows recapturing and repositioning within a safety margin of nearly 90% deployment (Figure 1).

Deployment Technique

The deployment process for the Pipeline Flex consisted of either pushing the device out of the catheter or unsheathing of the device. In contrast to the previous PED, deployment did not involve torqueing maneuvers since the distal sleeves allowed rapid release of the braids once the first 10 to 15 mm of the device were deployed and resheathing the device could be easily performed until the resheathing marker had reached the distal marker of the microcatheter (Figure 1). The device size was chosen based on the parent vessel measurements on the working angle views and the 3D angiogram. Technical nuances and advantages have been thoroughly described somewhere else.[8,10]

Dual antiplatelet therapy was performed in all institutions participating in the study but the drug regimen and monitoring for antiplatelet response was performed at the discretion of the facility.

Statistical Analysis

Outcomes were divided according to the 30-d modified Rankin Scale into favorable (mRS 0-2) and unfavorable (mRS 3-6). Continuous and binomial variables were correlated with outcome using Pearson's correlation test and for ordinal variables, the Spearman's rho test was used. Chi-Square test was used to determine the relationship between categorical variables. An exploratory analysis (univariate analysis) was performed to determine predictors of an unfavorable outcome. A stepwise multivariate logistic regression analysis was performed to determine predictors of the dependent variable, unfavorable clinical outcome (mRS 3-5). The accuracy of the logistic regression model was assessed by constructing a receiver operating characteristic curve. Statistical significance was defined as P value $\leq .05$. Statistical tests were performed with SPSS software (IBM SPSS Statistics for Windows, version 24.0. Armonk, New York).

RESULTS

Patient and Aneurysm Characteristics

A total of 205 patients with 223 unruptured aneurysms were treated with PED Flex (Medtronic) over a period of 18 mo. The mean age was 55.7 yr (±14.4 yr) and ranged

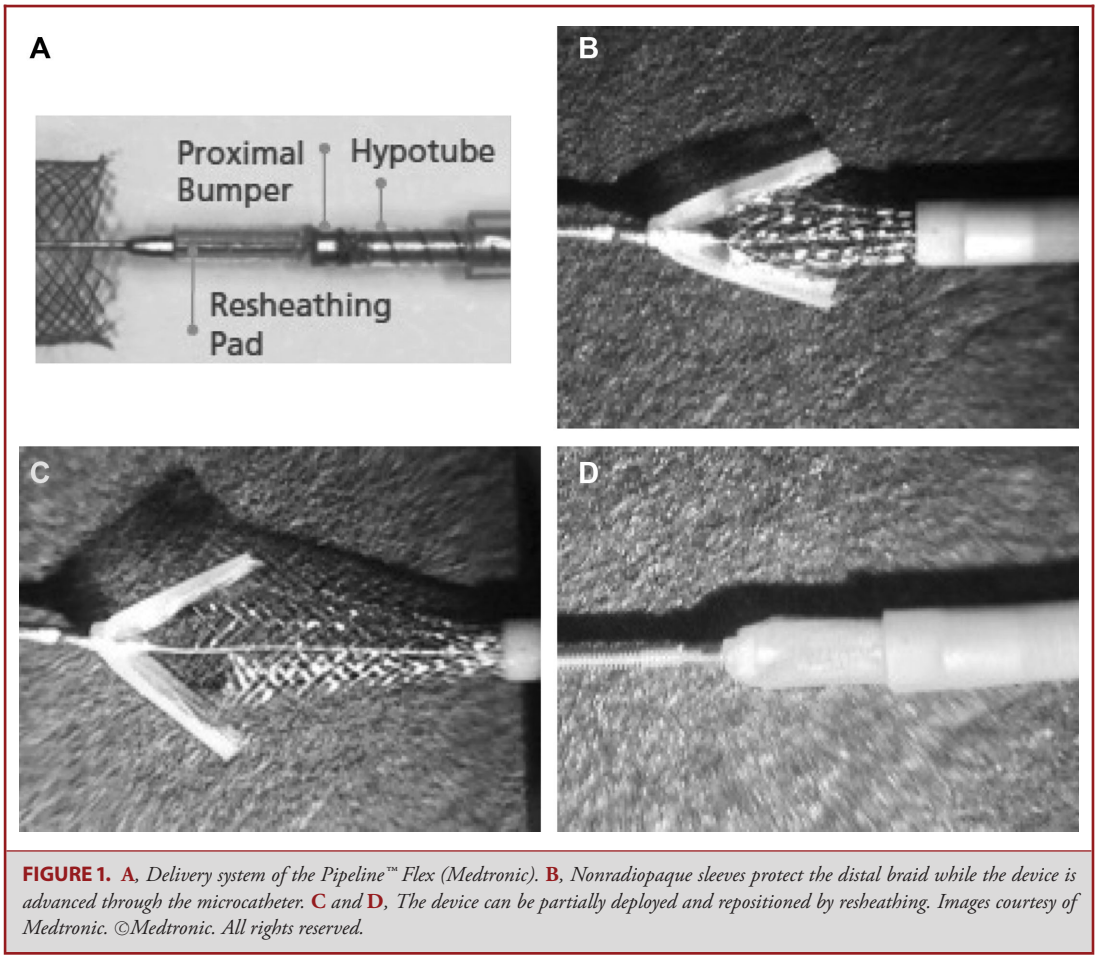

FIGURE 1. **A**, *Delivery system of the Pipeline™ Flex (Medtronic).* **B**, *Nonradiopaque sleeves protect the distal braid while the device is advanced through the microcatheter.* **C** *and* **D**, *The device can be partially deployed and repositioned by resheathing. Images courtesy of Medtronic. ©Medtronic. All rights reserved.*

from 18 to 86 yr. There were 165 females (80.4%). The majority of aneurysms were discovered incidentally (58.3%, 119/204) while the remaining lesions were referred for treatment due to previous history of subarachnoid hemorrhage (9.3%, 19/204), aneurysm recurrence (8.8%, 18/204), visual symptoms (5.9%, 12/204), and other symptoms presented in Table 1. One hundred seventy-seven aneurysms (79.3%, 177/223) were located along the ICA, 16 aneurysms (7.2%, 16/223) were in the anterior circulation distal to the ICA, and 30 aneurysms (13.5%, 30/223) were in the posterior circulation. One hundred fifty-five aneurysms (69.5%, 155/223) were saccular, 27 aneurysms (12.1%, 27/223) were fusiform, 10 aneurysms (4.5%, 10/223) were dissecting/pseudoaneurysm in appearance, and 31 aneurysms (13.9%, 31/223) were considered irregular (Table 1). The mean aneurysm size was 8.2 mm (±6.4 mm, range 1.0-40.0 mm). A total of 121 aneurysms (55.7%, 121/217) were small (≤7 mm), 89 lesions (41%, 89/217) were large (8-24 mm), and 7 aneurysms (3.3%, 7/217) were giant (≥25 mm). Eighteen aneurysms (8.8%) had previous treatment consisting of coiling in 6 lesions (33.3%), clipping in 3 (16.7%), first-generation PED in 2 (11.1%), and Woven Endobridge in 1 (5.6%). Previous treatment information was not available for 6 aneurysms.

Procedures

Successful PED Flex deployment was obtained in all procedures (100%). The 30-d neurological morbidity and mortality rate was 2.4% (5/205) with a 30-d neurological morbidity rate of 1.9% (4/205). All neurological morbidity and mortality occurred in anterior circulation aneurysms and consisted of ischemic events in 3 patients (1.5%) and intracranial hemorrhage in another patient (0.5%). The rate of intraprocedural events without neurological morbidity was 6.8% (14/205), consisting of intraprocedural ischemic events in 9 patients (4.5%) and hemorrhage in 5 patients (2.4%). Other technical events included difficulty capturing the delivery wire, which required a salvaging maneuver in 1 case (0.5%), retroperitoneal hematoma in 3 patients (1.5%), asymptomatic carotid dissection in 1 patient (0.5%), and device migration after deployment in another case (0.5%; Table 2). Multiple devices were employed in 53 aneurysms (24.4%, 53/217), and there was a correlation between the number

TABLE 1. Baseline Characteristics

Patients (n = 205)	Value (%)
Age (yr)	
Mean (±Std)	55.7 (±14.4)
Range	18-86
Gender	
Female	165 (80.4)
Male	40 (19.6)
Presentation	
Incidental	119 (58.3)
Previous SAH	19 (9.3)
Aneurysm recurrence	18 (8.8)
Visual symptoms	12 (5.9)
Headache	9 (4.4)
Mass effect	8 (3.9)
TIA	5 (2.5)
Other[a]	14 (6.8)
Aneurysms (n = 223)	**Value (%)**
Aneurysm size (mm)	
Mean (±Std)	8.2 (±6.4)
Range	1.0-40.0
Aneurysm type	
Small (≤7 mm)	121 (55.7)
Large (8-24 mm)	89 (41)
Giant (≥25 mm)	7 (3.3)
Aneurysm morphology	
Saccular	155 (69.5)
Irregular	31 (13.9)
Fusiform	27 (12.1)
Dissecting/Pseudoaneurysm	10 (4.5)
Aneurysm location	
ICA—Ophthalmic	61 (27.4)
ICA—Cavernous	27 (12.1)
ICA—PComm	27 (12.1)
ICA—Superior Hypophyseal	20 (9)
ICA—Supraclinoid	14 (6.3)
ICA—Paraophthalmic	8 (3.6)
ICA—Paraclinoid	7 (3.1)
ICA—Terminus	6 (2.7)
ICA—Cervical	4 (1.8)
ICA—Anterior choroidal	3 (1.3)
ICA—Petrous	1 (.4)
Middle cerebral artery	8 (3.6)
AComm	4 (1.8)
Anterior cerebral artery	3 (1.3)
Vertebral artery	18 (8.1)
PICA	6 (2.7)
Basilar artery	4 (1.8)
Posterior cerebral artery	2 (0.9)
Procedures	**Value (%)**
Multiple devices	53 (24.4)
Balloon angioplasty	36 (16.1)
Adjuvant coils	25 (11.2)
Resheathing	3 (1.4)

ICA, internal carotid artery; PComm, posterior communicating artery; PICA, posterior inferior cerebellar artery; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

[a]Other—information on presentation was not available.

of devices deployed and the aneurysm size ($R = .154$, $P = .02$). The highest use of multiple devices was in anterior circulation aneurysms (27%, 14/144) compared to 20% (6/30) in the posterior circulation. Overall, 2 devices were placed in 49 patients (23.9%), 3 devices were placed in 7 patients (3.4%), and 4 devices were used for 1 patient (0.5%). Information on resheathing maneuvers was available for 94.6% of the lesions (211/223) and was reported in 3 cases (1.4%), while adjuvant coiling and balloon angioplasty were employed in 25 (11.2%, 25/223) and 36 lesions (16.1%, 16/223), respectively. The device malposition rate was 0.5% (1/205) which resulted from a device migration after deployment.

Outcome Analysis

Information on discharge and 30-d mRS scores were available for 197 patients (96%) and 148 patients (72.2%), respectively. Favorable clinical outcome (mRS 0-2) was achieved in 186 patients (94.4%) at discharge and 140 patients (94.5%) at 30 d. Among the 11 patients with unfavorable outcome (mRS 3-6) at discharge, 7 had prior moderate to severe disability (mRS 3-4). When these patients were excluded from the analysis, a total of 4 patients (2.1%, 4/190) had loss of functional independence or death after treatment which corresponded to 2 patients living with moderate disability (mRS of 3), 1 patient with moderately severe disability (mRS of 4), and 1 death (mRS 6) in our patient cohort (mortality rate of 0.5%; Figure 2). Functional outcome at 6 mo was available for 58 patients (28.2%, 58/205) and was favorable (mRS 0-2) in all cases. During univariate analysis, the following variables were tested as predictors of unfavorable 30-d outcome: age ($P = .5$), gender ($P = .2$), aneurysm location ($P = .8$), aneurysm size ($P = .4$), number of devices deployed ($P = .3$), resheathing maneuvers ($P = .6$), adjuvant coiling ($P = .2$), balloon angioplasty ($P = .2$), and clinical complications ($P = .02$). During multivariate logistic regression analysis, however, we were unable to identify predictors of unfavorable outcome (Table 3). In addition, the only variables that demonstrated a correlation with 30-d mRS were aneurysm size ($R = .145$, $P = .04$), and complications during hospital stay ($R = .336$, $P = .0001$; Table 3).

Aneurysm Occlusion

Imaging follow-up was available for 92 lesions (41.2%, 93/223) at a mean time point of 4.8 mo, ranging from 0.5 to 9 mo. Based on the latest vascular imaging, 52.1% of the aneurysms (48/92) were completely occluded, 10.9% (10/92) had a small neck remnant, and 37% (34/92) had partial aneurysm filling. In-stent stenosis occurred in 6.4% (6/93) and was asymptomatic in all cases. Delayed device migration was not observed during the study.

DISCUSSION

Our results have demonstrated 30-d neurological morbidity and mortality rates of 1.9% and 0.5%, respectively. The majority of adverse events were ischemic strokes from thromboembolic

TABLE 2. Complications Based on Aneurysm Size and Location With PED Flex

	Small (<7 mm)	Large (8-24 mm)	Giant (>25 mm)	–
Anterior circulation	(n = 94)	(n = 62)	(n = 6)	–
Ischemic events	1	7	1	–
Hemorrhage	1	2	2	–
Technical complications	3	5	4	–
Posterior circulation	(n = 11)	(n = 17)	–	–
Ischemic events	1	2	–	–
Hemorrhage	0	0	–	–
Technical complications	1	2	–	–
Permanent complications	1	3	0	–
Transient complications	6	15	7	–
	Present Study	ASPIRe	IntrePED	PUFs
Morbidity and mortality rate	2.4%	6.8%	8.4%	5.6%
Neurological death	0.5%	1.6%	3.8%	2.8%

complications and all events occurred in anterior circulation aneurysms. Intracranial hemorrhage resulting in neurological morbidity occurred in 0.5% of patients. The rate of intraprocedural events without neurological morbidity was 6.8% and was similar across aneurysm locations (6.9% and 6.8% for anterior and posterior circulation aneurysms, respectively). These results are important as more neurovascular centers adopt the PED Flex (Medtronic) over the previous generation. We have shown that the PED Flex is safe in the periprocedural period (30 d) across multiple centers in the United States and have also demonstrated a lower rate of device malposition, 'corking' or misplacement requiring rescue maneuvers or removal. Several previous studies of the first-generation PED support our findings. During the IntrePED registry,[2] the 30-d neurological morbidity rate was 5.5% (44/793) and the 30-d neurological mortality rate was 2.5% (20/793). Data from a meta-analysis of flow diversion[11] prior to IntrePED included 1451 patients and 1654 aneurysms with estimated morbidity and mortality rates of 5% (95% confidence interval [CI], 4-7) and 4% (95% CI, 3-6), respectively. The rate of ischemic stroke during IntrePED was 4.7% (37/793) and estimated at 6% (95% CI, 4-9) in the meta-analysis, compared to 1.5% in our study. Similarly, the rate of symptomatic intracranial hemorrhage was 0.5% in the current study compared to 2.4% (19/793) during IntrePED and 3% (95% CI, 2-4) in the meta-analysis. The relatively low rate of ischemic events in our study may be partially attributed to increased experience with flow diverters with modern antiplatelet agents. The mechanisms of intracranial hemorrhage after flow diversion, however, remain largely speculative and may be a result of multiple factors including hemorrhagic transformation of distal ischemic stroke, overinhibition of P2Y12 receptors by dual antiplatelet therapy, and emboli from foreign-body reaction.[12-14]

One of the advantages of the PED Flex lies in the ability to resheath the device and reposition into the desired landing zone reliably. The previous generation PED had a steeper learning curve compared with standard stent-coil techniques. Jabbour et al[7] recognized the initial learning curve with PED in their institutional experience. Their rate of procedural complications decreased from 14.5% to 7.4% ($P = .2$) after their first 55 interventions and the rate of major complications decreased from 7.2% to 0% ($P = .04$). The modifications in the delivery system might ease the learning curve for PED interventions and its new design may potentially reduce the rate of intraprocedural events related to device deployment. Our results showed a device malposition rate of 0.5% (1/205) which was the result of a device migration after deployment. Moreover, there were no cases of device removal, malfunction, or incomplete deployment. Previous studies have shown a higher malposition rate with the first-generation PED ranging from 4.9% (6/123) to 14.3% (6/42).[15-17] Similar to our findings, a recent study found a significant decrease in the rate of deployment failure with the PED Flex (7.1%, 3/42) compared to the first-generation PED (23.9%, 17/71, $P = .03$).[18] Still, deployment of the PED Flex is not without technical nuances and operators should keep in mind that the device cannot be fully opened if oversized at the distal landing zone or if the parent vessel is too small to accommodate it.

Despite testing multiple variables to predict unfavorable outcome at 30 d, we did not find statistical significance on logistic regression analysis. Previous studies have found that previously treated aneurysms (odds ratio [OR] = 4.9, 95% CI, 1.1-20),[7] female gender (OR = 5.7, $P = .04$), and posterior circulation (OR = 10.5, $P = .01$)[19] were predictive of increased morbidity and mortality with the first-generation PED. One of the potential explanations was the low rate of events resulting in unfavorable outcome (2.1%, 4/190) which might have decreased our ability to detect the observation. Moreover, our results were supported by a prior study which analyzed predictors of poor clinical outcome (mRS > 1) in patients treated with the first-generation PED in comparison to stent-assisted coiling[20] and also found that none of the variables included were predictive of outcome. Analysis of the IntrePED data showed that the rates of procedure-related

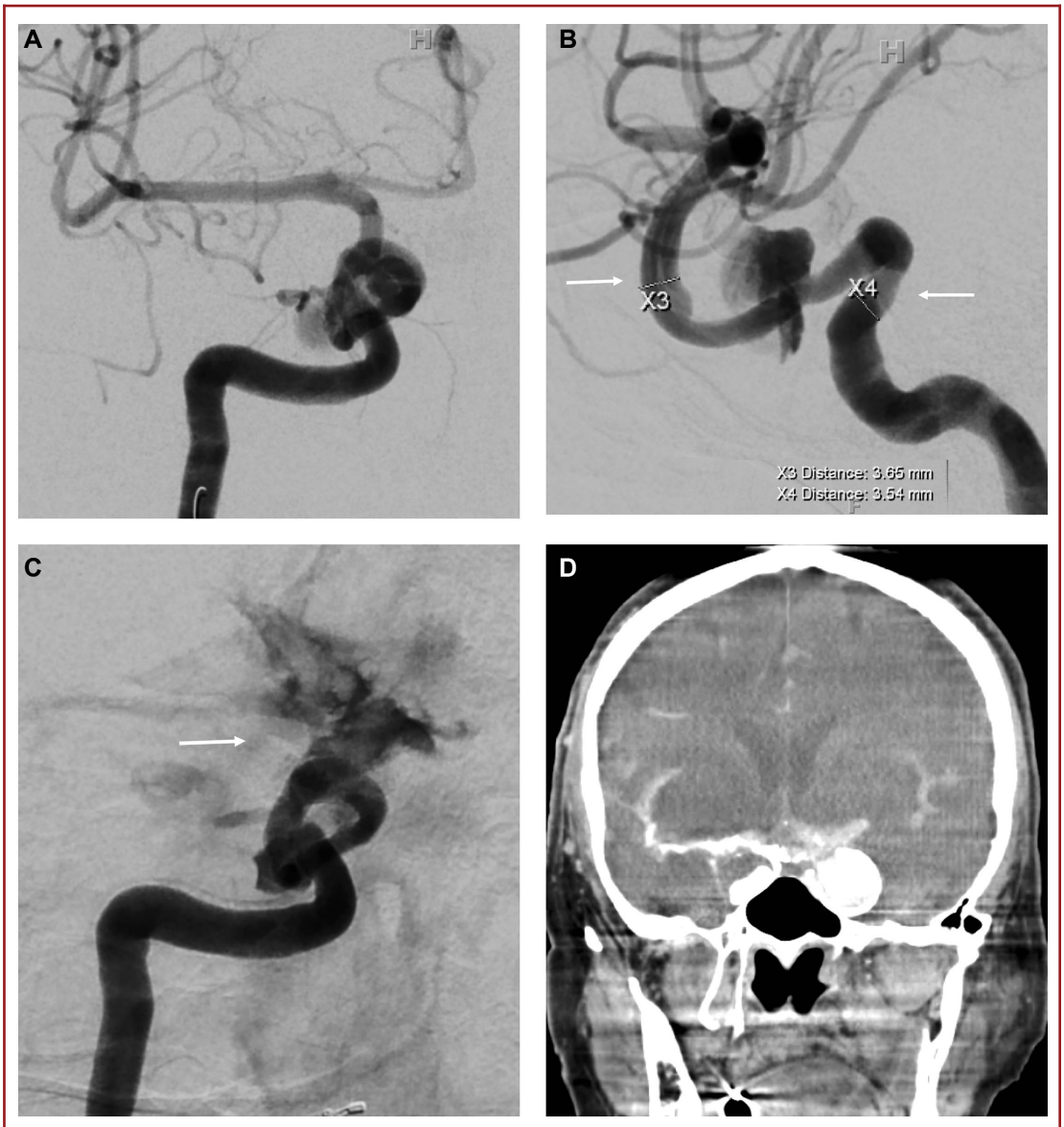

FIGURE 2. *An elderly patient with bilateral symptomatic giant cavernous ICA aneurysms had undergone treatment of a right lesion with a 3.5 × 18 mm Pipeline classic (Medtronic) 8 mo prior. Follow-up imaging showed persistent filling of the right aneurysm and previous attempts to treat the left aneurysm failed because the lesion could not be traversed for deployment with a flow diverter. A 3.75 × 20 mm Pipeline Flex (Medtronic) was deployed telescoping the previous right ICA device and balloon-dilation was performed with a 4.0 × 10 Hyperglide catheter (Medtronic) to improve apposition. During this maneuver, a longitudinal rupture of the distal ICA occurred which resulted in a fatal hemorrhage.* **A**, *Digital subtraction angiography (DSA) of the right internal carotid artery in AP view demonstrating persistent contrast filling of the right cavernous ICA aneurysm 8 mo after treatment with Pipeline classic.* **B**, *DSA in lateral view depicting measurements of the proximal and distal parent artery (white arrows) in preparation for Pipeline Flex placement.* **C**, *DSA showing contrast extravasation distal to the Pipeline Flex (white arrow) which occurred after balloon-dilatation of the device.* **D**, *CT angiography after the ICA rupture demonstrating diffuse subarachnoid hemorrhage and vessel dissection.*

morbidity and mortality were higher for giant and difficulty-to-treat aneurysms (posterior circulation, dissecting, and fusiform). Our study found a correlation between aneurysm size and 30-d mRS ($R = .145$, $P = .04$, Figure 3) which, although cannot be used to infer a causal relationship, indicates that a potential relationship might exist, reinforcing the view that large and giant aneurysms often portend a worse prognosis after flow diversion compared to smaller lesions.

TABLE 3. Logistic Regression Analysis of Predictors of Unfavorable Outcome (30-d mRS > 2)

Univariate analysis		*P* value
Age (yr)		.50
Gender		.21
Aneurysm size		.43
Aneurysm location		.83
Number of devices		.32
Adjuvant coils		.21
Balloon angioplasty		.21
Resheathing		.67
Complications		**.02**[a]
Multivariate analysis	**95% CI**	***P* value**
Complications	0.01-.059	.01[a]
Correlation of functional outcome after treatment with Pipeline Flex	***R* value**	***P* value**
Age	.069	.38
Gender	.011	.87
Aneurysm location	.025	.72
Aneurysm size	.145	**.04**
Aneurysm morphology	.047	.50
Multiple aneurysms	.024	.73
Multiple devices	.004	.95
Complications	.336	**.0001**
Adjuvant coils	.041	.56
Balloon angioplasty	.011	.87
Resheathing	–.035	.62

[a]Bold values denote statistical significance.

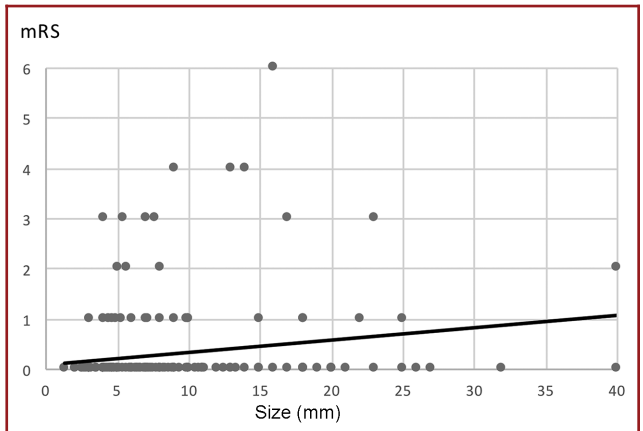

FIGURE 3. *Correlation of aneurysm size and mRS score after treatment with Pipeline Flex (Medtronic).*

Limitations

Limitations of the study included its retrospective nature and inherent biases associated with this design such as selection bias, lack of control group, and missing data points to name a few: the neck size was not measured, differences in treatment protocol with PED Flex varied across the institutions in the study, and insufficient follow-up in several patients. Our study was designed to assess immediate procedural outcomes and technical events with PED Flex and thus the long-term rates of clinical events and aneurysm occlusion were not evaluated. In addition, we did not evaluate the type of catheters (intermediate and distal) used for deploying the PED, which could have contributed with the periprocedural outcomes. Also, there was no independent review for imaging follow-up and each center was responsible for data collection and imaging assessment. Given that the PED Flex has retained the same device design and composition to its earlier counterpart, one could infer that aneurysm occlusion rates would remain similar to the first-generation PED. However, it is important to highlight that the majority of aneurysms treated in this study were smaller than 10 mm contrary to those treated in the PUFS trial but similar to the ASPIRe and IntrePED studies. We also had a high proportion of ICA aneurysms compared to other more frequent locations such as anterior communicating or MCA bifurcation which should be taken into consideration when generalizing our results. Also, our exploratory analysis for unfavorable outcomes had suboptimal statistical power and was not adjusted to other variables.

CONCLUSION

Our study suggests that treatment of intracranial aneurysms with the PED Flex (Medtronic) has low rates of neurological morbidity and mortality at 30 d. In addition, technical events related to device deployment were also low, most likely due to the latest modifications in the delivery system.

Disclosures

Dr Nelson, Dr Moran, and Dr Tassku are consultants for Medtronic. Dr Linfante is a consultant for Medtronic, Stryker, and Penumbra and a stock holder for Surpass, InNeuroCo, and Three Rivers. Dr Turk is a consultant for Stryker, Covidien, Penumbra, Microvention, Medina Medical, and Three Rivers Medical; he is a stockholder for Medina Medical and Three Rivers. Dr Siddiqui is a consultant for Codman, Medtronic, Guide Point Global Consulting, Penumbra, Stryker, MicroVention, W.L Gore & Associates, Three Rivers Medical Inc, Corindus Inc, Amnis Therapeutics Ltd, CereVasc LLC, Pulsar Vascular, The Stroke Project Inc, Cerebrotech Medical Systems Inc, Rapid Medical, Lazarus (acquired by Medtronic), Reverse Medical (acquired by Medtronic), Covidien (acquired by Medtronic), Neuravi, Silk Road Medical, and Rebound Medical; he has financial interests with StimSox, Valor Medical, Neuro Technology Investors, Cardinal, Medina Medical Systems, Buffalo Technology Partners Inc, and International Medical Distribution Partners. Dr Levy is a consultant for Pulsar and Blockade Medical LLC; a shareholder/Ownership Interest with Intratech Medical Ltd, Blockade Medical LLC, and NeXtGen Biologics; National PI for SWIFT PRIME Trials (Covidien/Medtronic); receives honorarium for training and lectures from Covidien/Medtronic; is on the AIS Clinical Advisory Board for Stryker; and Serves on The Advisory Board for NeXtGen Biologics and MEDX. Ricardo Hanel is a consultant for Covidien, Stryker, Codman, and Microvention as well as a shareholder for InNeuroCo. The other authors have no personal, financial, or institutional interests in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Becske T, Kallmes DF, Saatci I, et al. Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. *Radiology*. 2013;267(3):858-868.
2. Kallmes DF, Hanel R, Lopes D, et al. International retrospective study of the pipeline embolization device: A multicenter aneurysm treatment study. *Am J Neuroradiol.* 2015;36(1):108-115.
3. Kallmes DF, Brinjikji W, Boccardi E, et al. Aneurysm Study of Pipeline in an Observational Registry (ASPIRe). *Intervent Neurol*. 2016;5(1-2):89-99.
4. Yu SC, Kwok CK, Cheng PW, et al. Intracranial aneurysms: midterm outcome of pipeline embolization device–a prospective study in 143 patients with 178 aneurysms. *Radiology*. 2012;265(3):893-901.
5. Saatci I, Yavuz K, Ozer C, Geyik S, Cekirge HS. Treatment of intracranial aneurysms using the pipeline flow-diverter embolization device: A single-center experience with long-term follow-up results. *AJNR Am J Neuroradiol.* 2012;33(8):1436-1446.
6. Rangel-Castilla L, Cress MC, Munich SA, et al. Feasibility, safety, and periprocedural complications of pipeline embolization for intracranial aneurysm treatment under conscious sedation. *Neurosurgery*. 2015;3(11 Suppl):426-430.
7. Jabbour P, Chalouhi N, Tjoumakaris S, et al. The Pipeline Embolization Device: learning curve and predictors of complications and aneurysm obliteration. *Neurosurgery*. 2013;73(1):113-120.
8. Pereira VM, Kelly M, Vega P, et al. New Pipeline Flex device: initial experience and technical nuances. *J NeuroIntervent Surg*. 2015;7(12):920-925.
9. Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. *Stroke*. 2001;32(9):1998-2004.
10. Aguilar-Salinas P, Brasiliense LB, Gonsales D, et al. Evaluation of Pipeline Flex delivery system for the treatment of unruptured aneurysms. *Expert Rev Med Dev*. 2016;13(10):885-897.
11. Brinjikji W, Murad MH, Lanzino G, Cloft HJ, Kallmes DF. Endovascular treatment of intracranial aneurysms with flow diverters: A meta-analysis. *Stroke*. 2013;44(2):442-447.
12. Cruz JP, Chow M, O'Kelly C, et al. Delayed ipsilateral parenchymal hemorrhage following flow diversion for the treatment of anterior circulation aneurysms. *AJNR Am J Neuroradiol.* 2012;33(4):603-608.
13. Hu YC, Deshmukh VR, Albuquerque FC, et al. Histopathological assessment of fatal ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid aneurysms with the Pipeline Embolization Device. *J Neurosurg*. 2014;120(2):365-374.
14. Delgado Almandoz JE, Crandall BM, Scholz JM, et al. Last-recorded P2Y12 reaction units value is strongly associated with thromboembolic and hemorrhagic complications occurring up to 6 months after treatment in patients with cerebral aneurysms treated with the pipeline embolization device. *AJNR Am J Neuroradiol.* 2014;35(1):128-135.
15. Kan P, Siddiqui AH, Veznedaroglu E, et al. Early postmarket results after treatment of intracranial aneurysms with the pipeline embolization device: a U.S. multicenter experience. *Neurosurgery*. 2012;71(6):1080-1088.
16. Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the intracranial treatment of aneurysms trial. *AJNR Am J Neuroradiol*. 2011;32(1):34-40.
17. Lin LM, Colby GP, Kim JE, Huang J, Tamargo RJ, Coon AL. Immediate and follow-up results for 44 consecutive cases of small (<10 mm) internal carotid artery aneurysms treated with the pipeline embolization device. *Surg Neurol Int*. 2013;4(1):114.
18. Le EJ, Miller T, Serulle Y, Shivashankar R, Jindal G, Gandhi D. Use of Pipeline Flex is associated with reduced fluoroscopy time, procedure time, and technical failure compared with the first-generation Pipeline embolization device. *J Neurointerv Surg*. published online ahead of print: May 9, 2016.
19. O'Kelly CJ, Spears J, Chow M, et al. Canadian experience with the pipeline embolization device for repair of unruptured intracranial aneurysms. *AJNR Am J Neuroradiol.* 2013;34(2):381-387.
20. Chalouhi N, Starke RM, Yang S, et al. Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. *Stroke*. 2014;45(1):54-58.

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