JVIN Journal of Vascular and Interventional Neurology
OFFICIAL JOURNAL OF THE ZEENAT QURESHI STROKE INSTITUTE

Comparative Analysis of Unruptured Cerebral Aneurysm Treatment Outcomes and Complications with the Classic versus Flex Pipeline Embolization Devices and Phenom versus Marksman Microcatheter Delivery System: the Role of Microcatheter Choice on Complication Rate

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Abstract

Objective—The second-generation pipeline embolization device (PED), flex, has improved opening and resheathing ability compared to the first-generation classic PED device. A previously reported single-institutional study suggests that the PED flex devices are associated with lower rates of complications. However, there was limited discussion regarding the complication rate with respect to microcatheter choice for PED delivery and deployment. The present study aims to evaluate outcomes of aneurysm treatment with PED flex versus classic along with the Phenom microcatheter versus Marksman microcatheter.

Methods—A retrospective, IRB-approved database of all patients who received a PED classic or PED flex device between January 2012 and July 2018 was analyzed. Microcatheter choice, patient demographics, medical comorbidities, aneurysm characteristics, treatment information, and outcome data were analyzed using univariate analyses.

Results—A total of 75 PED procedures were analyzed. There was no significant difference in major complications between the PED classic and PED flex. However, those treated using the Marksman microcatheter were more likely to have a major complication (periprocedural hemorrhage or ischemic event; 16.6% vs. 0%, $p = 0.0248$) than those treated with the Phenom microcatheter. Within the PED flex cohort, all major complications were associated with the Marksman microcatheter ($p = 0.0289$).

Conclusions—The present study does not replicate significantly fewer complications with PED flex but demonstrates a significant reduction in complications with the Phenom microcatheter. Ultimately, this suggests multiple factors are involved in achieving positive outcomes and low complication rates in PED treated unruptured cerebral aneurysms.

Introduction

The pipeline embolization device (PED) is used to occlude aneurysms that are less amenable to coiling, stent-assisted coiling, and surgical clip. Evidence from multicenter clinical series, including the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial [1], Intre-PED study [2], and ASPIRe registry [3], has shown high rates of aneurysm occlusion with low rates of recurrence and periprocedural complications similar to other endovascular procedures [1–3]. However, the first-generation Classic PED device, Food and Drug Administration (FDA) approved in 2011, has been criticized for difficulties with the deployment mechanism, subsequently leading to procedural complications (e.g. stroke, intracranial hemorrhage, subarachnoid hemorrhage, intragenic dissection) [4–7].

The second-generation PED Flex, FDA approved in 2015, was designed to address these concerns. It features improved opening and the ability to be resheathed compared to the first-generation classic PED device. Fur-

Vol. 11, No. 1, pp. 13–18. Published January, 2020

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thermore, the pusher wire was changed to a laser-cut hypotube for enhanced pushability. Recent studies have suggested that the PED flex devices are associated with improved outcomes, demonstrating both reduced procedural times [8] and lower rates of complications [9,10]. In one study, Colby *et al.* [9] showed major morbidity or death in 1.9% with PED flex compared to 5.6% with the PED classic. It also reported ischemic strokes in 1.3% compared to 2.8% and hemorrhage in 1.6% compared to 3.6% between the PED flex and classic, respectively [9]. However, no study to date provides analysis of complication rate with respect to microcatheter choice for PED delivery and deployment. The present study aims to evaluate outcomes of aneurysm treatment with PED flex versus classic along with the Phenom microcatheter versus Marksman microcatheter.

Methods

Patient selection and data collection

After obtaining IRB approval, a retrospective chart review was performed to identify all patients who received PED classic or PED flex devices between January 2012 and July 2018. Eligible patients were ≥18 years of age and had unruptured intracranial aneurysms located in the posterior or anterior circulation. The cohort was split into groups based on the type of PED. Patients who received multiple PED devices for multiple unruptured aneurysms were analyzed as a separate procedure if they received the second PED device more than 3 months after the initial PED. Two patients with extracranial, cervical internal carotid artery (ICA) aneurysms treated with PED were excluded from our analysis. Aneurysms considered for PED were large or giant wide-necked aneurysms of the cavernous and paraclinoid segments of the ICA as per the original FDA premarket approval indications for use, although in certain cases, the device was deployed in other locations and used to treat aneurysms <10 mm when it was thought to be a better option.

Electronic medical records and radiographic images for all included patients were examined to identify patient demographics, medical comorbidities, aneurysm characteristics, treatment factors, and outcome data. Aneurysm characteristics included location, shape, and size as defined by pretreatment diagnostic cerebral angiography. Treatment factors included number of PED devices used, adjuvant coiling, P2Y12 reaction unit (PRU) at treatment and at time of complication if applicable, and microcatheter choice. Outcome data included the presence of intraprocedural hemorrhage, thrombosis, vasospasm, periprocedural ischemic stroke, subarachnoid hemorrhage, intraparenchymal hemorrhage, postoperative residual aneurysm, dissection, and need for retreatment.

Patient management

Patients underwent general anesthesia for all cases, and periprocedural heparinization was titrated to maintain activating clotting times of 1.5–2.5 times baseline. For unruptured aneurysms, patients first underwent noninvasive vascular imaging and in certain cases pretreatment diagnostic cerebral angiography. Patients were started on dual-antiplatelet therapy (DAT; aspirin 81 mg and clopidogrel 75 mg) 7–14 days before their scheduled intervention and titrated to obtain a target PRU value of 100–200. Ticagrelor 90 mg was used in cases of when patients had low clopidogrel response.

Before PED placement, diagnostic cerebral angiography was performed. Three-dimensional rotational angiography was used to better delineate aneurysmal morphology and to determine the optimal working projections. Some procedures included adjunctive coil embolization. Postdeployment angiography was assessed for degree of initial occlusion. Satisfactory placement was obtained with one device in most cases; however, some cases required the use of an additional device (i.e., for very large aneurysms, if there was significant taper between the proximal and distal landing zones, when deployment of the first device was suboptimal, or when additional coverage across the neck was deemed necessary). Postprocedurally DAT was used as the standard antiplatelet regimen of postinterventional prophylaxis for 6 months and, after 2013, was titrated to obtain a PRU of 100–200 (routine PRU testing was not available at our institution prior).

Statistical analyses

Statistical analyses were performed using GraphPad (GraphPad Software Inc., La Jolla, CA, USA) and Microsoft Excel (Microsoft Inc., Redmond, WA, USA). Data are presented as frequency for categorical variables and means with ranges for continuous variables. To analyze differences between PED flex and PED classic groups and the Marksman and Phenom microcatheter groups, univariate analyses were completed using unpaired t-test and ANOVA tests. The Marksman and Phenom microcatheters were compared because of their exclusive use at our home institution.

Results

A total of 75 PED procedures (35 PED classic and 40 PED flex; 27 cases with the Phenom microcatheter and 48 with the Marksman microcatheter) were analyzed.

Patient demographics

There were no significant differences in demographic features between the PED classic and flex groups. The average age of patients who received the PED classic was 52.9 compared to 48.4 in the PED flex group. Each group had a high percentage of females with 89% and 85% in the classic and flex groups, respectively. Comorbidities, including hypertension, smoking, diabetes, and COPD were similar across both groups. 40% of all patients were smokers.

Aneurysm characteristics

85% of the aneurysms treated were of the ICA. Other locations included the anterior communicating (ACoA), middle cerebral (MCA), posterior communicating (PCoA), basilar, and vertebral arteries. A significantly higher portion of saccular aneurysms were treated with PED classic (p = 0.036). Conversely, a significantly greater proportion of complex aneurysms were treated with the PED flex (p = 0.04). The average size of aneurysms treated with the PED classic was marginally larger than those treated with the PED flex (p = 0.061).

Treatment factors

PRU at the time of treatment averaged around 140 for both groups. PRU at time of complication did not vary significantly between groups or from the time of treatment PRU with an average of 133. The Marksman microcatheter was used in 100% of PED classic cases and only 33% of PED flex cases (p = 0.0001). There was no significant difference in frequency of cases requiring >1 PED or adjuvant coiling.

Outcome measures

There was no significant difference in major complications (periprocedural hemorrhage and ischemic events) between the PED classic and PED flex. However, those treated using the Marksman microcatheter were more likely to have a major complication (periprocedural hemorrhage or ischemic event; p = 0.0248) than those treated with the Phenom microcatheter. Follow-up was on average 12.4 months. See Table 2. Within the PED flex cohort, all major complications occurred with the Marksman microcatheter (p = 0.0289). See Table 3. No complications were reported in cases that utilized the Phenom microcatheter.

Table 1. Summary data of demographics, aneurysm features, treatment factors, and outcomes in patients who received PED classic or PED flex

Characteristics	Classic	Flex	Both	*p*-value
Demographics				
Age	52.9	48.4	50.7	0.2752
Female	31 (89)	34 (85)	65 (87)	0.6498
Hypertension	19 (54)	20 (50)	39 (52)	0.7109
Diabetes mellitus	5 (14)	5 (13)	10 (13)	0.8204
Smoker	15 (43)	15 (38)	30 (40)	0.6366
COPD	3 (9)	4 (10)	7 (9)	0.8319
Aneurysm features				
Left	20 (57)	19 (48)	39 (52)	0.4043
Location				
ACoA	1 (2.9)	2 (5)	3 (4)	0.6366
ICA	29 (83)	35 (88)	64 (85)	0.5707
MCA	0 (0)	1 (2.5)	1 (1.3)	1
PCoA	2 (5.7)	1 (2.5)	3 (4)	0.4785
Basilar	2 (5.7)	0 (0)	2 (2.7)	0.2144
Vertebral	1 (2.9)	1 (2.5)	2 (2.7)	0.9236
Shape				
Saccular	32 (91)	29 (73)	61 (81)	0.0358
Blister	1 (2.9)	3 (7.5)	4 (5.3)	0.372
Dissecting	1 (2.9)	1 (2.5)	2 (2.7)	0.9236
Complex	1 (2.9)	7 (18)	8 (11)	0.0404
Size, mm	10.68	7.35	8.85	0.0611
Treatment factors				
>1 PED used	4 (11.4)	1 (2.5)	5 (6.7)	0.1219
Adjuvant coiling	9 (26)	7 (18)	16 (21)	0.3151
PRU at treatment	146	138	140	0.7401
PRU at time of complication	165	101	133	0.2909
Marksman microcatheter	35 (100)	13 (33)	48 (64)	0.0001
Outcomes				
Thrombosis	3 (8.6)	1 (2.5)	4 (5.3)	0.3031
Intraprocedural hemorrhage	2 (5.7)	0 (0)	2 (2.7)	0.2144
Dissection	3 (8.6)	1 (2.5)	4 (5.3)	0.3031
Vasospasm	13 (37)	13 (33)	26 (35)	0.6733
Intimal hyperplasia	4 (11)	6 (15)	10 (13)	0.6498
Periprocedural ischemic stroke	2 (5.7)	0 (0)	2 (2.7)	0.2144
Subarachnoid hemorrhage	2 (5.7)	2 (5)	4 (5.3)	0.8907
Intraparenchymal hemorrhage	1 (2.9)	1 (2.5)	2 (2.7)	0.9236
Residual aneurysm	3 (8.6)	0 (0.0)	3 (4)	0.0969
Retreatment	2 (5.7)	0 (0.0)	2 (5.7)	0.2144
Length of follow-up (months)	16.9	8.4	12.4	0.0024

Discussion

Recent studies have evaluated the effectiveness and safety profile of the PED flex to compare it with the multiple trials evaluating PED classic. In 2013, the initial study evaluating the safety and efficacy of the PED classic, the PUFS trial demonstrated 99.1% complete occlusion rate of large or giant wide-necked ICA aneurysms after 180 days with a 5.6% prevalence of major ipsilateral stroke or neurological death [1]. In the later IntrePED trial, Kallmes *et al.* [2] found a neurologic morbidity and mortality rate of 8.4% with an ischemic stroke rate of 4.7%, and an intracranial hemorrhage rate of 2.4%. Similarly, the ASPIRe reported major neurological morbidity of 6.8% with an ischemic stroke rate of 4.7% and hemorrhage rate of 3.7% [3].

Given the recent FDA approval of the flex PED, there is less data evaluating its effectiveness in comparison to the classic; however, two major case series have recently been published [9,10]. A multicenter study looking at 223 aneurysms found a neurologic morbidity (symptoms

Table 2. Summary data of outcomes for patients treated with the Marksman or Phenom microcatheter

Characteristics	Marksman	Phenom	*p*-value
Outcomes	48	27	
Thrombosis	4 (8.3)	0 (0)	0.1068
Intraprocedural hemorrhage	2 (5.7)	0 (0)	0.2823
Dissection	4 (8.3)	0 (0)	0.1068
Vasospasm	19 (40)	7 (26)	0.2329
Intimal hyperplasia	6 (12.5)	4 (14.8)	0.8246
Periprocedural ischemic stroke	2 (5.7)	0 (0)	0.2823
Subarachnoid hemorrhage	4 (8.3)	0 (0)	0.1068
Intraparenchymal hemorrhage	2 (4.2)	0 (0)	0.2823
Residual aneurysm	3 (8.6)	0 (0)	0.1849
Retreatment	2 (5.7)	0 (0)	0.2823
Major complications (periprocedural hemorrhage and ischemic stroke)	8 (16.6)	0 (0)	0.0248

Table 3. Summary data of major complications for patients treated with the Marksman or Phenom microcatheter within the PED flex cohort

Characteristics	Marksman	Phenom	*p*-value
Major Complications	13 (total)	27 (total)	
Periprocedural ischemic stroke	0 (0)	0 (0)	1.000
Subarachnoid hemorrhage	2 (15.3)	0 (0)	0.1000
Intraparenchymal hemorrhage	1 (7.7)	0 (0)	0.3250
Major complications total (periprocedural hemorrhage and ischemic stroke)	3 (23.1)	0 (0)	0.0289

Table 4. Comparison of number of major complications

Comparison type	Number of major complications (A vs. B)	*p*-value
PED classic vs. flex	5 3	0.4611
Marksman vs. phenom microcatheter	8 0	0.0248
Marksman vs. phenom microcatheter within PED flex cohort	3 0	0.0289

lasting greater than 7 days) and mortality rate of 2.4% with ischemic stroke in 4.5% and hemorrhage in 2.4% [10]. It should be noted that these numbers present any intraprocedural events, even if they did not result in neurological morbidity. Similarly, in a single-institution series, Colby *et al.* [9] looked at 568 cases and found a rate of major morbidity or death in 1.9% with PED flex compared to 5.6% with the PED classic. It also reported ischemic strokes in 1.3% compared to 2.8% and hemorrhage in 1.6% compared to 3.6% between the PED flex and classic, respectively [9]. At present that Colby *et al.* offer the only case series that directly compares the PED flex and classic within the same dataset. Of note, its complication rate for the classic PED is substantially lower than previous PED classic multicenter trials.

In our case series, the PED flex had a 100% success rate compared to 94.3% with the PED classic. This is similar to previous studies that noted an increased success rate and lower retreatment need with the PED flex [9,10]. However, in contrast to previous results, there was no significant difference in major complications between the PED classic and PED flex [9,10]. Furthermore, in contrast to previous studies, our data demonstrate that those using the Marksman microcatheter were more likely to have a major complication (periprocedural hemorrhage or ischemic event; $p = 0.0248$) than those treated with the Phenom microcatheter. Even within the PED flex cohort, there was a higher complication rate with the Marksman microcatheter compared to no complications with the Phenom microcatheter. No complications were reported in any cases that utilized the Phenom microcatheter.

The Marksman microcatheter for PED delivery has been previously described as unable to provide the necessary support for delivery of the PED flex, reliable deployment of the implant, or consistent resheathing of the device [11]. Compared to the PED classic, the PED flex has decreased flexibility secondary to the improvements in deployment and resheathability of the device. Consequently, the use of a microcatheter with a distal flexible tip in addition to a decreased size difference between the proximal and distal outer diameter is thought to be more supportive for the delivery microcatheter of PED flex [11]. A case series detailing the experience of using the VIA27 (Microvention, Tustin, CA, USA) described success deployment of the PED flex in 127 cases despite significant cervical ICA tortuosity and moderate to severe cavernous ICA tortuosity [11]. Similarly, it is possible that the increased distal flexibility of the Phenom microcatheter compared to the Marksmen microcatheter improves PED delivery, resulting in less complications. The association between microcatheter use and complication rate has not been reported in the analyses of other PED flex studies. Colby *et al.* [9] noted that they used the Marksman microcatheter in 95% of PED classic cases and subsequently used the VIA27 microcatheter for 56% of PED flex cases. Bivariate analysis looking at use of VIA27 as a predictor of major complications was nonsignificant and analysis of the Marksman as a predictor was not performed [9].

Although the use of the Marksman has decreased substantially in the setting of advancing microcatheter technology and increased use of products like the Phenom and VIA27, the association between microcatheter use and PED outcomes suggests a multifactorial contribution to the improved outcomes seen with PED flex. Consequently, other components such as Platelet Function P2Y12 (PRU) levels were also considered in our analysis.

Studies assessing optimal PRU levels associated with minimal ischemic and hemorrhagic events have been looked at with the classic PED [12–14]. While some studies show that PRU levels are predictive of perioperative ischemic and hemorrhage events [12–14], others show that there is no relationship [13]. There has not been a clear consensus on whether PRU levels are important in preventing complications, or on a specific level that is associated with minimal risk of ischemic and hemorrhagic events. The present study found no significant difference in PRU levels at the time of major complications compared to preprocedural PRU levels and did not observe any differences between the PED classic and flex groups. The role of optimizing PRU levels in minimizing ischemic and hemorrhagic events remains unclear.

There are possible alternative explanations for the difference in complication rates observed with the Marksman compared to the Phenom microcatheter. An important consideration is the temporal association of the microcatheter use with increased experience with PED. Jabbour *et al.* [4] previously demonstrated a steep learning curve with PED classic where they observed a complication rate of 16.2% in the first third of 109 patients and 5.6% in the last third. It is possible that the more recent use of the Phenom corresponds with increased user experience with PED and consequently improved outcomes. The existence of a steep learning curve has also been postulated as an alternative explanation for the observed differences in complication rates between the PED flex and classic [9]. However, our study also demonstrated a statistically significant difference in complications between the Marksman and Phenom microcatheter with PED flex only cases, suggesting that system interactions with the device play a role in ease of deliverability and patient outcomes.

It should also be noted that a significantly higher portion of saccular aneurysms were treated with PED classic ($p = 0.036$). Conversely, significantly more complex aneurysms were treated with the PED flex ($p = 0.04$). Given that complex aneurysms have been shown to be associated with higher rates of complications and worse outcomes [15,16], this could serve as a possible explanation to explain why the present study did not duplicate lower complication rates with the PED Flex.

Potential limitations include the smaller number of cases in the present case series compared to those previously published. Overall, the rate of complications, including periprocedural ischemic stroke, subarachnoid hemorrhage, and intraparenchymal hemorrhage, were 14.2% and 7.5% for the PED classic and flex, respectively. Given that the PED classic was associated with a higher frequency of major complications, the lack of significance may suggest that the present study was not powered to recognize this difference. The increasing complexity of PED flex cases may mask improvement in outcomes compared to the PED classic. Further limitations include its retrospective design and its associated biases, including incomplete data points and possible selection biases. Additionally, the study was intended to look at short-term outcomes, focusing primarily on periprocedural complications, consequently limiting its ability to access long-term outcomes. Although long-term follow-up spanned an average of over a year for both groups, data collection focused on features of the aneurysm rather than the quality of life measures.

Conclusions

The present study does not replicate previous findings of significantly fewer complications with PED flex but demonstrates a significant reduction in complications with the Phenom microcatheter. Given the Phenom's later use compared to the Marksman, increased operator experience likely contributes to this finding. However, the difference in complications seen in Flex only cases suggests that system choice does play a role. Ultimately, this suggests multiple factors are involved in achieving positive outcomes and low complication rates in PED treated unruptured cerebral aneurysms. System selection with the new PED flex device is an important factor to consider as this study demonstrates.

Acknowledgments:

None.

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