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Research Article

The Pipeline: Less is More, Slower is Better, and Smaller is Possible

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Abstract

Background and Purpose: Despite experience gained with the Pipeline Embolization Device (PED), the following remain unclear: the significance of intra-procedural aneurysm occlusion after PED placement, if PED's should be used for treatment of smaller aneurysms, and whether multiple PED's are needed to achieve occlusion.

Methods: Between October 2009 and December 2015, 299 patients, with 342 aneurysms distributed at the internal carotid artery and posterior circulation underwent PED embolization by a single team. Data was collected prospectively and analyzed retrospectively. A new metric assessing flow into the aneurysm following PED placement was created: the Post Stenting Flow Scale (PSFs). It ranges from 0 (no residual flow) to 3 (no significant change in flow). Clinical complications, as well as aneurysm occlusion rates and their predictors, were calculated.

Results: The overall peri-procedural clinical complication rate was 18/299 (6%) including 2.7% mortality. All mortality occurred in the giant and fusiform groups. Predictors of clinical complication were aneurysm location (posterior vs. anterior circulation) and the use of multiple PED's. Clinical complications were more common in fusiform and giant aneurysms 15/168 (9%) than in other aneurysms 3/131 (2.2%). PSFs of 0 was a predictor of vascular complications. Occlusion rate was 77%. PSFs was its only significant predictor.

Conclusions: Using a single PED for aneurysm embolization is enough. Rapid and total occlusion of the aneurysm following PED deployment is an ominous sign and warrants clinical attention. Expanding the use of PED's to treat smaller aneurysms located at the internal carotid artery appears to be a valid strategy.

Keywords: aneurysm**;** stent**;** device

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Introduction

The introduction of the Pipeline embolization device (PED, Covidien/Medtronic, Irvine, CA) was a revolution in the treatment of intracranial aneurysms. The initial approval of the PED was restricted to the adult population, for giant aneurysms at the extradural internal carotid artery (ICA); however, with experience, expansion of its original indication was inevitable.

A few important questions concerning the PED remain. What is the optimal number of PED's needed to treat an aneurysm? Should coils be used in conjunction with PED embolization? The current literature indicates lack of consensus[1-2]. What is the significance of rapid aneurysm occlusion following PED placement? Does it predict complications or aneurysm occlusion? PED's are now frequently used beyond the initial indications, for aneurysms less than 15 mm and pediatric patients. The answer to the following question is still lacking: In the aneurysms amenable to both techniques, what is the merit of PED vs. coiling?

Materials and methods

This is a retrospective analysis of prospectively collected data on PED embolization at N.N. Burdenko Neurosurgery Research Institute in Moscow, from October 2009 through December 2015. Data collection and transfer was approved through the ethics committee without obtaining consent from the subjects. Ethics committee and guardian consent were obtained to place minors on Aspirin and Plavix. Data included patient demographics, size and location of aneurysms, size and number of PED's used per aneurysm, vascular and clinical complications, andclinical and angiographic follow up.

Patients received double anti-platelet therapy: 75 mg of clopidogrel and 100 mg of aspirin for 3-7 days prior to treatment. Patients were kept on clopidogrel for 6 months. Its efficacy was assessed prior to surgery using anti-platelet agents on the platelet function with INNOVANCE PFA-200 (Siemens) aggregometer using collagen and epinephrine (for screening), collagen and adenosine diphosphate (ADP) (for aspirin), and P2Y12 (for clopidogrel) cartridges. The goal was aggregation time exceeding 300 seconds. Forclopidogrel resistance, ticagrelor was administered at 180 mg/day. PED was sizedat 0.25 mm larger than the parent vessel, and activated clotting time (ACT) was > 250 seconds.

Follow-up included digital cerebral angiography (DCA), computed tomography angiography (CTA), or magnetic resonance angiogram. For follow-up obtained at an outside institution, images and/or a written report were sent back.

The size of each aneurysm was characterized as small (≤ 5 mm), medium (6-15 mm), large (16-25 mm), giant (> 25 mm), or fusiform. Location was divided into ICA-extra-Dural (ICA-Extra), ICA-intra-Dural (ICA-ID), and posterior circulation. In the anterior circulation there was only 1 aneurysm distal to the ICA bifurcation. Age was categorized into four groups: < 20, 21- 40, 41-60, and > 60 years.

Peri-procedural clinical complications (1-30 days) were calculated per patient, and included mortality, hemorrhagic/ischemic stroke, and transient ischemic attack (TIA), excluding groin complications. A delayed clinical complication rate was determined by worsening of function from before the procedure to the clinical follow-up based on the modified Rankin Scale (mRS) score. Clinical follow-up was obtained during the first angiographic follow-up or a phone call (range: 1-60 months).

Vascular complications included vessel rupture, ischemic stroke, parent vessel occlusion (PVO), or significant slowing of blood flow in the parent vessel due to dissection or severe vasospasm.

Predictors of aneurysm occlusion following treatment were analyzed. Occlusion rate was calculated from acceptable imaging assessment obtained in one of three ways: based on all available information (angiographic imaging studies and/or report); reports and images for patients with available DCA; and angiographic imaging

studies sent to the primary institution.

A system was created to assess post-PED blood flow into the aneurysm: Post-Stenting Flow Scale (PSFs) ranging from 0 to 3. For no flow, the PSFs score was 0. The PSFs was 1 for very slow residual flow, 2 for slight but definite slowing of the flow, and 3 for no change in flow to the aneurysm. PSFs scores were either analyzed based on the full scale or dichotomized: 0 and 1 vs. 2 and 3. PSFs score was ascribed by one author (SA).

Statistical analysis

Rates were evaluated for demographics, vascular complications, peri-procedural and delayed clinical complications, mortality, and aneurysm occlusion. Stepwise binary logistic regression methods were used to analyze factors associated with peri-procedural clinical complications, vascular complications, aneurysm occlusion, and PSFs (0 and 1vs. 2 and 3). Factors analyzed included age, sex, aneurysm size, aneurysm location, PSFs (dichotomized or using entire scale), use of balloon into the PED straightening, dilatation into the PED, addition of coil, removal of the PED, and number of PED's left in place (assessed as more than one left in place vs. 1 or 0 left in place). Statistical significance was set at $p < 0.05$, with $p \leq 0.10$ required for inclusion in the stepwise regression. SPSS Statistics software (IBM) was used for data analysis.

Results

302 patients were available for the study. In three patients (with four aneurysms), the operator was unable to successfully catheterize the parent vessel and the procedure was aborted, leaving 299 patients with 309 vessels and 342 aneurysms in the study cohort. Three subjects (with 3 aneurysms) were unsuccessfully treated. Of the 339 aneurysms treated with at least 1 PED, 214 aneurysms had imaging follow up (63%), 6 of them had significant artifacts on imaging rendering them unsuitable for interpretation, leaving 208 aneurysms for assessment of occlusion rate. Average age was 49.2 years (range: 12-77, ten patients under the age of 18). 224 (75%) were female. All of the subjects were Caucasian. Fifty-one (14.9%) were small aneurysms, 48 (14.0%) medium, 74 (21.6%) large, 141 (41.2%) giant, and 28 (8.3%) fusiform (Table 1).

Table 1 Characteristics of aneurysms (n = 342)

Size	No. (%)	Clinical Complications (%)*	Occlusions (%)†
Small	51 (14.9)	0/19 (0%)	20/25 (80%)
Medium	48 (14.0)	1/44 (2.2%)	30/34 (88.2%)
Large	74 (21.6)	2/71 (2.8%)	30/42 (71.4%)
Giant	141 (41.2)	9/150 (6.0%)	66/94 (70.2%)
Fusiform	28 (8.3)	6/33 (18.2%)	13/13 (100%)
Location			
ICA Extra	205 (60)		
ICA ID	103 (30)		
Posterior	34 (10)		

*Clinical complications (n = 299); †Occlusions (n = 208); ICA: internal carotid artery; ID: intra dural

Clinical Outcomes

Peri-procedural complications were found in 18 (6%) patients, divided as follows: 9 (3%) ischemic strokes, 5 (1.6%) hemorrhagic strokes, and 4 TIA's (1.3%). Mortality rate was 8/299 (2.7%): 5 due to rupture of aneurysm/parent vessel, 3 due to ischemic stroke. Excluding the 8 mortality cases in the peri-procedure time frame, of the remaining 291 patients, 227 patients (74%) had a clinical follow-up evaluation beyond one month. Of those, 7 patients expired (3.3%) and 15 (7%) became clinically worse. Of the total 15 deaths known in this cohort, all occurred in patients with a fusiform or giant aneurysm.

Posterior aneurysms were found to have the highest percentage of peri-procedural complications (24%). Logistic regression confirmed that patients with aneurysms located in the ICA Extra or ICA ID were less likely to have clinical complications than aneurysms in a posterior location (odds ratio < 0.20, Table 2). Having more than one PED left in a single vessel, as compared to 0 or 1 PED left, was also significantly correlated with peri-procedural complications (odds ratio = 3.2).

Table 2 Logistic regression model for peri-procedural clinical complications (n=299)

Variables	OR (95% CI)	P-Value
Location (ICA Extra vs Posterior)	0.15 (0.05 – 0.46)	0.001
Location (ICA ID vs Posterior)	0.16 (0.04 – 0.66)	0.01
Multiple PED vs 0,1 PED left in place	3.2 (1.0 – 10.0)	0.04

OR: Odds ratio; CI: Confidence interval; ICA: internal carotid artery; ID: Intra dural

Aneurysm size was significantly correlated with peri-procedural complications, but only for univariate analysis. The clinical complications rate was 22% (6/27) for fusiform aneurysms. The clinical complications rates were 6% (9/141), 3% (2/69), 2% (1/43), and 0% (0/19) for the giant, large, medium and small aneurysms, respectively. For < 15 mm aneurysms, the complication rate was 1.6% (1/62).

Of the 227 patients with clinical follow-up (1-60 months) there were 20 mortalities and further strokes (8.5%). All except one occurred in giant and large aneurysms for a total of 14.5% morbidity and mortality.

The cohort included 10 pediatric patients (range 12-18 years) with symptomatic aneurysms (12-41 mm). One mortality, one permanent neurological deficit, and one TIA were recorded. All complications occurred in patients with either giant or fusiform aneurysms during the peri-procedural time frame.

Vascular Complications

Vascular complications were found in 18/309 (6%) vessels. The most frequent vascular complication was PVO (6 cases). Flow scale was significantly correlated with vascular complications (Table 3). A flow scale score of 0 was

associated with increased vascular complications compared to 1 and 2 (odds ratio < 0.2 for 1 and 2 vs. 0 as the control).

Table 3 Logistic regression model for vascular complications (n = 309)

Variables	OR (95% CI)	P-Value
Flow scale (1 vs 0)	0.15 (0.05 - 0.45)	0.001
Flow scale (2 vs 0)	0.17 (0.01 - 1.0)	0.006
Flow scale (3 vs 0)	0.12 (0.54- 13.42)	0.053
Addition of Coil	3.5 (0.8 – 15.9)	0.10

OR: Odds ratio; CI: Confidence interval

Table 4 Occlusion rates of aneurysms treated with 1PED per vessel and with angiographic imaging (1st follow-up)

	Ratio (%)
Occlusion Rate	146/189 (77)
Occlusion Rate with DCA	43/63 (75)
Occlusion Rate by Size	
Small	16/18 (83)
Medium	30/33 (91)
Large	28/39 (72)
Giant	61/86 (71)
Fusiform	7/7 (100)
Occlusion Rate by PSFs	
0,1	94/115(82)
2,3	52/74 (70)

PSFs: Post-Stent Flow Scale; DCA: Digital Cerebral Angiography

Aneurysm Occlusion

Occlusion rate of aneurysms treated using a single PED was calculated using three different cohorts. 189 aneurysms had either angiographic images or written reports; of them, 146 had total occlusion (77%). Sixty-three had angiographic images that were available for direct interpretation (S-A), with 43 (68%) showing total occlusion. Thirty-eight aneurysms had a DCA at follow-up, with 27 (71%) totally occluded. Due to the fact that occlusion rates were similar for all three calculations, we adopted the rate of the largest sample size: 77% (Table 4).

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PSFs: Post-Stent Flow Scale; DCA: Digital Cerebral Angiography

Fusiform aneurysms had the highest occlusion rate at 100% (7/7). All occurred within 20 months. Giant aneurysms had the lowest occlusion rate of 71% (Table 4). Of the 189 aneurysms, 123 were located in the ICA-Extra, with total occlusion for 95 (77%) at the first follow-up. A total of 38/51 (75%) aneurysms located in the ICA-ID occluded and 13/15 (87%) aneurysms located in the posterior circulation occluded.

Logistic regression analyzing factors correlated with occlusion for all aneurysms with imaging and at least one PED at the first follow up (n = 208) demonstrated that only PSFs was significantly related to total occlusion. Aneurysms with PSFs of 2 or 3 were associated with less total occlusion at follow-up compared to PSFs of 0 or 1 (odds ratio = 0.51, confidence interval = 0.27 – 0.99, p-value = 0.047). Use of a balloon was also included in the regression but did not reach statistical significance (p = 0.07).

There were 34 aneurysms treated with more than one PED. Of them, 17 had total angiographic imaging follow-up, with 13 (76%) demonstrating total occlusion.

8 pediatric patients had imaging follow-up (6-65 months). All exhibited total occlusion at imaging follow-up (100%).

Blood Flow following PED deployment

The only variable that was significantly related to dichotomized PSFs was the size of the aneurysm. Based on binary logistic regression of all aneurysms with sufficient imaging at the first follow up and a PSFs score (n = 205), the odds of a PSFs of 2 or 3 with a giant aneurysm was 0.3 times the odds with a small aneurysm (Table 5).

Table 5 Logistic regression model for blood flow (PSFs) (n=205)

Variables	OR (95% CI)	P-Value
Medium vs. small	1.0 (0.4-2.9)	0.94
Large vs. small	0.4 (0.1-1.1)	0.09
Giant vs. small	0.3 (0.1-0.8)	0.02
Fusiform vs. small	2.1 (0.5-8.6)	0.31

OR: Odds ratio; CI: Confidence interval

Discussion

The peri-procedural clinical complication rate of 6%, including 2.7% mortality, and overall aneurysm occlusion rate of 77% are in agreement with the reported literature[3-4]. We identified several new findings. Using multiple PED's correlated with clinical complications, without an increase in likelihood of aneurysm occlusion. Adding coils did not significantly enhance the chance of aneurysm occlusion. A decrease in flow after PED deployment based on the PSFs (0, 1) correlated with occlusion of the aneurysm at follow-up; however, PSFs = 0 correlated with a significant increase in vascular complication rate. It also had an increase in clinical complications albeit not statistically significant. All mortalities and most morbidity occurred in giant and fusiform aneurysms with peri-procedural complications of 1.6% for aneurysms less than 15 mm, although size was not correlated with complication rate for multivariable analysis. Sex was not significantly correlated with any of the output parameters.

Aneurysm embolization using PED "Less is More"

Few authors have reported using coils in addition to PED's without increased complicationrates[5-6]. Some authors went further in advocating this technique for a theoretical advantage of adding protection to the aneurysm dome[2, 7-9]. Using this combined technique, Lin et al. reported a significantly higher proportion of aneurysm occlusions when comparing a PED plus coils to a PED alone, with a similar complication rate[2]. Our data do not support this assertion. In multivariable logistic regression, adding coils did not enhance the chances of aneurysm occlusion, while it was correlated with the vascular complications. Our data argues against the use of coils in addition to PED's.

Placing multiple PED's was correlated with clinical complications, without enhancing the aneurysm occlusion rate. Patients with more than one PED left in a single vessel were 3.2 times more likely to have peri-procedural complications than patients treated with one or zero PED's. Similar to our results, other authors found that using multiple PED's for aneurysm embolization was an independent predictor of clinical complications without an increase in aneurysm occlusion rate[1, 10]. They also reported a 3-fold increase in clinical complication rate in the multiple vs. singlePED group (15% vs. 5%, respectively), with almost identical aneurysm occlusion rates

in both groups: 87% vs. 84%, respectively. Their results indicate that using a single PED, without the addition of coils, provides the optimal strategy. It seems that when it comes to PED aneurysm embolization, "less is more."

Aneurysm occlusion using PED "Slower is better"

The importance of rapid and significant changes in the aneurysmal blood flow immediately following PED deployment is not mentioned in the literature. In this series, 12% of vessels exhibited PSFs of 0 shortly following PED deployment. Briganti et al.[4], in their flow diverter meta-analysis reported immediate aneurysm occlusion rate (corresponding to our PSFs = 0) after placing a different kind of flow diverter in 1704 aneurysms of 10.8% (Range 2-18.2%), similar to our results.In the current cohort, patients with PSFs of 0had a significantly higher chance for vascular complications compared to PSFs of 1 or 2, and nearly significant for PSFs = 3 (Table 3). The only predictor of PSFs was aneurysm size, where giant aneurysms had a higher chance of developing PSFs of 0 when compared to small (less than 5 mm) aneurysms. In our cohort, giant aneurysms had a higher complication rate than smaller aneurysms, albeit not statistically significant, which was more convincingly demonstrated by other authors[3-4, 11]. It is not clear why certain giant aneurysms develop this dreadful complication while other equal size aneurysms do not. We postulate that it may be due to different hemodynamic changes in the parent vessel and inside the aneurysm following PED deployment. Another reason could be the status of the cerebral collaterals and how much the ipsilateral hemisphere is dependent on the parent vessel flow. For example, a hemisphere with good collaterals supplying incoming flow through the anterior communicating artery will help shut down a weak flow coming through the ICA following PED implantation. Most likely, however, the reasons are multifactorial.

These data point to the fact that the development of PSFs of 0 is a serious occurrence; after all, the major benefit of the different flow diverters is preservation of the parent vessel. The operator must take extra precautions when using PED's, especially in giant aneurysms, such as demanding higher antiplatelet inhibition tests and aiming for a higher ACT (above 300s), or having platelet glycoprotein (GP) IIb/IIIa receptor antagonists such as Abciximab (Reo Pro) available. Furthermore, PSFs scores were correlated with aneurysm occlusion on follow-up angiogram. PSFs was the only significant predictor of aneurysm occlusion on follow-up imaging in this series.

The case for expansion of PED indications; smaller aneurysms, younger patients:

Our data demonstrate that PED's can safely treat aneurysms on the ICA less than 15 mm. There was 1 clinical complication in 62 patients and 99 aneurysms (1.6%), which compares favorably with different coiling technique complication rateof 4%-19%[12-15].In the International Retrospective Study[3], a subgroup of 349 saccular (less than 10 mm) aneurysms, all were on the ICA in the subgroup of unruptured saccular aneurysms; the neurological morbidity and mortality was 3.6%, which matches our findings. Another retrospective study[16], comparing PED embolization to coiling techniques in less than 10 mm aneurysms, demonstrated a similar complication rate and occlusion rate in both arms (5% vs. 3%, respectively) and with similar occlusion rate (80% vs. 70%), respectively. These findings indicate that PED embolization of small (less than 15 mm),unruptured ICA aneurysms may be as safe as the different coiling techniques.

In our series and others[16],the occlusion rate in this subgroup of aneurysms was encouraging at 85%, which is close to the rate reported using different stent-assisted coiling[13,17]. There was only 1 delayed clinical complication in aneurysms < 15 mm out of 49 (mRS changed from 1 to 2 at 1-year). This finding indicates that delayed complications are rare in this subgroup.

Before advocating the use of PED to treat this group,a few important points should be emphasized. First, our results apply only to the ICA, a vessel without perforators; we had only one aneurysm in our series distal to the ICA bifurcation. We have already shown here, and in agreement with other authors, that PED embolization in the vertebro-basilar system carries a higher risk, and we should be prudent before advocating the use of PED in this territory. Second, we still need to answer the following question: What do you do if the follow-up cerebral

angiogram demonstrates persistent filling of the aneurysm? The only valid approach we will have is to add more PED's. Would this be enough to ultimately achieve aneurysm occlusion, and how many PED's per session will be needed? Third, following PED embolization there is a need for a dual antiplatelet therapy for a few months while the aneurysm is not occluded. This carries a 2.5% risk of significant hemorrhage per year[18]. Is this a justified risk? Two randomized trials are currently underway comparing coiling to PED embolization in this aneurysm population: Flow Diversion in the Intracranial Aneurysm treatment (FIAT)[19] and Flow Diversion versus Traditional GDC Based Endovascular Therapy[20]. These results will be very relevant.

The number of pediatric patients was small, yet the largest published to date. Based on the low rate for mortality and permanent disability, it seems that extending the use of PED's to the pediatric population is safe and feasible.

This study has a few limitations: it is retrospective, and there is a lack of uniformity and consistency of imaging follow-up (DCA, CTA, and MRA). In addition, 21% of patients were lost to follow-up, and an imaging study was not available for direct evaluation in every case. Nonetheless, our results match the reported literature remarkably concerning the complications and aneurysm collusion rate.

Conclusion

Using one PED alone for aneurysm embolization is probably the best strategy. Rapid and total aneurysm occlusion following PED deployment is an ominous sign. Treating aneurysms smaller than 15 mm in the ICA is possible and safe.

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Data Sharing

The raw data is available upon request from the corresponding author.

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