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ORIGINAL RESEARCH

Silent ischemic events after Pipeline embolization device: a prospective evaluation with MR diffusion-weighted imaging

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ABSTRACT

Background The development of ischemic events is relatively common after endovascular interventions, and flow diverters may pose a particular threat owing to their increased technical complexity and high metal content.

Objective To investigate the incidence and potential risk factors for thromboembolic lesions after treatment with a Pipeline embolization device (PED).

Methods This prospective study included a total of 59 patients electively treated with a PED over 12 months. Postprocedural diffusion-weighted imaging sequences of the brain were obtained 24 h after interventions to detect ischemic lesions. Demographic data, aneurysm characteristics, antiplatelet management, and perioperative data were correlated with the rate of ischemic events.

Results The incidence of silent ischemic events after use of a PED was 62.7% (37 patients) and neurological symptoms occurred in 8.1% of affected patients. Development of ischemic events was significantly associated with older patients (≥60 years; p=0.038). Routine use of platelet function assays and newer P2Y12 receptor inhibitors (ticagrelor) were not associated with fewer thromboembolic events.

Conclusions Thromboembolic events are relatively common after treatment with a PED with an incidence comparable to stent-assisted and conventional coiling but the risk of neurological morbidity from ischemic burden is low. Older patients are at particularly increased risk of thromboembolic events.

INTRODUCTION

Flow diverters are widely recognized as a major advancement in the treatment of intracranial aneurysms. These stent-like constructs were designed with a higher-density mesh than other aneurysm-specific intracranial stents, providing higher metal surface area coverage when fully deployed inside the vessel. After the construct is in place, flow diverters have been shown to disrupt the inflow jet inside the aneurysm and trigger a cascade of events leading to aneurysm occlusion and neo-endothelialization across the aneurysm neck.[1] Flow diverters can be particularly advantageous in side-wall aneurysms considered unsuitable for conventional endovascular techniques (coiling or stent-coiling) or lesions with a high surgical risk. However, placement of flow diverters is not without limitations and clinical studies have highlighted an increased risk of thromboembolic complications associated with their use.[2 3] The risk of transient ischemic attack or stroke after use of flow diverters can be estimated based on reports from multiple studies,[2–4] but the incidence of silent ischemic injuries following a Pipeline embolization device (PED) procedure remains unclear, and there is increasing evidence that the cumulative burden of ischemic brain injury might cause minor deficits or aggravate vascular dementia.[5] In light of these facts, this study was undertaken to determine the incidence of silent thromboembolic events following treatment with a PED (Covidien Vascular, Mansfield, Massachusetts, USA) in two high-volume neurovascular centers and to analyze demographic data, aneurysm characteristics, and technical variables that might contribute to an increased risk of ischemic complications.

PATIENTS AND METHODS

Patient population

Over the course of 12 months, patients treated with a PED at two institutions in the USA (Mayo Clinic, Jacksonville and Mayo Clinic, Rochester) underwent routine postprocedural MRI after placement of flow diversion. Data on these patients were prospectively collected as part of a quality insurance program (tables 1 and 2). Local institutional review boards approved the study. Patients included had received PED treatment for unruptured intracranial aneurysm in the anterior and posterior circulation. Patients were excluded in cases of contraindications to MRI or recent subarachnoid hemorrhage. Data obtained for analysis included patient's demographic information (gender/age), dual antiplatelet regimen, aneurysm characteristics (location/size), and number of devices used. The incidence of neurological morbidity was also determined based on clinical course until hospital discharge.

MRI protocol

As part of the study protocol, all patients received brain MRI with diffusion-weighted imaging (DWI), T1/T2, and fluid-attenuated inversion recovery (FLAIR) 24 h after the procedure. The MRI was performed using a 3 Tesla system and DWI consisted of multisection, single-shot, spin-echo, echo-planar imaging sequences. Diffusion gradients were applied in each of the x, y, and z directions with two b values (0 and 1000 s/mm^2). Imaging

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Table 1 Patient population

Characteristics	Number (%)
Gender	
Female	48 (81.4)
Male	11 (18.6)
Age (years)	
<60	31 (52.5)
≥60	28 (47.5)
Aneurysm location	
Internal carotid artery (cavernous to posterior communicating segment)	57 (81.4)
Middle cerebral artery	1 (1.4)
Anterior cerebral artery	1 (1.4)
Anterior communicating artery	1 (1.4)
Basilar/vertebral artery	6 (8.6)
Posterior inferior cerebellar artery	3 (4.3)
Superior cerebellar artery	1 (1.4)
Aneurysm size (mm)	
<7	45 (64.3)
7–12	11 (15.7)
13–24	8 (11.4)
≥25	6 (8.6)
Number of devices	
1 PED	53 (89.8)
2–3 PEDs	4 (6.8)
≥4 PEDs	2 (3.4)

PED, Pipeline embolization device.

parameters included a field of view of 24 cm, a 116×97 matrix, TE 69 ms, section thickness 5 mm, and an intersection gap 1 mm. Two experienced physicians (DM—neuroradiology and RH—neurosurgery) evaluated the MRI images, reaching consensus on abnormalities detected on DWI sequences. No inter-observer variability testing was performed. Ischemic lesions on DWI sequences (DWI+) were further examined to determine their vascular territory and relationship to the PED procedure (ipsilateral or contralateral to the device) as well as the number of DWI+ lesions. Patients who underwent diagnostic angiography within 7 days before PED intervention were analyzed separately.

Antiplatelet regimen

The protocol for dual antiplatelet therapy differed slightly between the two institutions and provided the opportunity to study its effect on silent embolic events after PED. At Mayo Clinic, Jacksonville patients typically received aspirin (325 mg/day) and clopidogrel (75 m/day) 5 days before the expected date of the procedure. Individual response to the antiplatelet regimen was measured in every patient using aspirin assay and P2Y12 assay (Accumetrics VerifyNow, San Diego, California, USA) before intervention. Patients with a subtherapeutic response to clopidogrel (>240 P2Y12 reaction units (PRU)) received a loading dose of ticagrelor (180 mg) and the P2Y12 assay was repeated in approximately 2 h, whereas individuals who were not compliant with the antiplatelet schedule received a loading dose of aspirin (650 mg) and clopidogrel (600 mg) on the morning of the procedure and the P2Y12 assay was repeated in 4 h. If response to the loading dose of clopidogrel was inadequate, ticagrelor was initiated. We consider this strategy highly effective because ticagrelor is one of the most effective inhibitors of the P2Y12 receptor and drug resistance has not been identified.[6] At Mayo Clinic, Rochester, patients received aspirin and clopidogrel before intervention and individual P2Y12 responses were not measured and therefore non-responders were not identified.

Pipeline procedure

The technique for PED deployment was similar in both institutions and performed by experienced neurosurgeons and interventional neuroradiologists. Arterial access was obtained, and then an initial intravenous bolus of heparin (50 units/kg) was administered and additional heparin given to obtain an activated clotting time >200 s throughout the procedure. Heparinization was discontinued but not reversed at the conclusion of the procedure. PED deployment was performed under general endotracheal anesthesia with the aid of biplane angiography units. Three-dimensional rotational angiography was routinely carried out. The size of the device was selected according to the measurements of the inflow vessel.

Femoral access was obtained with a 5 French (F) introducer sheath, and a 5F DAV catheter was placed in the proximal segment of the common carotid artery. The 5F short vascular sheath and diagnostic catheter were exchanged for a 7F short vascular sheath and the guiding catheter (6F Neuron, 070; Penumbra, Alameda, California. USA) or a 6F long sheath was placed in addition to a 058 Navien (ev3, Irvine, California, USA). A Marksman (ev3, Irvine, California, USA) microcatheter was advanced distal to the landing zone and the device was deployed across the neck of the aneurysm using a combination of unsheathing of the device and advancement of the insertion wire. Expansion of the PED was closely monitored with fluoroscopy or DynaCT angiography after final deployment. When the device seemed inadequately opposed to the vessel wall, balloon angioplasty (Hyperglide or Hyperform; ev3 Neurovascular, Irvine, California, USA) of the device was performed. Coverage of the abnormal vessel segment with one device was the primary goal in each procedure to avoid multiple coverage of clinically significant side branches. Contrast stasis inside the

Table 2 Incidence and risk factors for silent ischemic events on DWI after treatment with PED

Study	No. of patients	No. of aneurysms	Incidence of DWI+ lesions (%)	Incidence of TIA/stroke (%)	Risk factors
This study	59	70	62.7	5.1	Age ≥60 years
Heller *et al*[19]	23	26	52	0	Size ≥10 mm
Iosif *et al* [14]	38	49	81.6	13.2	None
Tan *et al*[15]	74	57	50.9	6.8	Female gender
Total	177	202	61.5	6.7	–

DWI, diffusion-weighted imaging; PED, Pipeline embolization device; TIA, transient ischemic attack.

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aneurysm was expected but not pursued. However, multiple devices were used when the aneurysm neck could not be covered completely with a single device.

Statistical analysis

All statistical analyses were performed using SAS V.9.1 or higher (SAS Institute Inc, Cary, North Carolina, USA). Information is presented for categorical variables as frequency and percentage and for continuous variables as means and SD. Association between demographic data, aneurysm characteristics and number of DWI+ events and comparison of DWI+ events between the two institutions were completed using t tests. A Wilcoxon test was used to investigate the association between aneurysm size, location, and DWI+ events. Statistical significance was defined as a p value <0.05.

RESULTS

Demographics and DWI lesions

Over the course of the study, a total of 59 patients harboring 70 intracranial aneurysms were consecutively treated with PED and included in the MRI protocol. The patient population consisted of 48 women and 11 men with a mean age of 59 years (range 31–85 years). Sixty aneurysms were located in the anterior circulation (85.7%) and 10 lesions were located in the vertebrobasilar system. The mean aneurysm size was 6 mm (range 1.3–40 mm). Indications for treatment of smaller lesions included, in most instances, recurrent aneurysms following previous coiling. Overall, ischemic lesions were identified on DWI in 37 of the 59 patients (62.7%) and a total of 197 DWI lesions were recognized. The distribution of the lesions in the distal vasculature suggested embolic phenomena in all cases. Eight of the 37 patients had only one DWI+ lesion (21.6%), 19 patients had 2–5 DWI+ lesions (51.4%), four patients had 6–10 DWI+ lesions (10.8%), five patients had 11–20 DWI+ lesions (13.5%), and one patient had more than 21 DWI+ lesions (2.7%). The mean number of DWI+ lesions per patient was 5.2 (±5.8) lesions. In 22 (59%) of the 37 patients with DWI+ on MRI, the lesions were located exclusively ipsilateral to the site of the PED procedure. In one of the 37 DWI+ patients (2.7%), the lesions were located exclusively contralateral to the intervention. A total of 152 DWI+ lesions (77.2%) were located ipsilateral to the site of PED deployment, 31 DWI+ lesions (15.7%) were located contralateral to the PED, and 12 DWI+ lesions (6.1%) were located in the posterior circulation after treatment with PED for anterior circulation aneurysms. Four patients (10.8%) developed DWI+ lesions in all three vascular locations evaluated in the study (ipsilateral, contralateral, and posterior circulation). Diagnostic angiography within 7 days before the PED procedure was performed in seven patients of the cohort (11.9%). In this group, no DWI+ lesions were found in three patients. One patient developed ipsilateral DWI+ lesions and three patients developed DWI+ lesions contralateral to the PED procedure. Three of the 59 patients included in the study (5.1%) developed neurological events after the procedure. These events resulted in dysarthria after emergence from anesthesia following treatment of a vertebrobasilar junction aneurysm, rupture of the aneurysm, and subarachnoid hemorrhage 5 days after treatment of a giant ophthalmic segment aneurysm, resulting in persistent right hemiparesis and left inferior quadrantanopia. Finally, a patient with a small ophthalmic segment aneurysm developed slurred speech, facial numbness, and memory loss after treatment. DWI+ lesions were identified in these patients (3/37).

Predictors of DWI+ events

Differences in antiplatelet management and P2Y12 testing between the participating institutions were not significantly associated with an increased number of ischemic lesions after the PED procedure. In 45 consecutive patients tested for antiplatelet response before intervention, 27 (60%) developed DWI+ events, whereas 10/14 patients (71.4%) developed ischemic events in the protocol where no testing was performed ($p=0.54$; 95% CI −3.37 to 1.81). A total of 161 DWI+ lesions were found in patients tested for P2Y12 response, of which 119 (73.9%) DWI+ lesions (72.7%) were ipsilateral, 30 lesions (18.6%) were contralateral, and 12 lesions (7.4%) were located in the posterior circulation. In contrast, a total of 36 DWI+ lesions were found in patients without platelet assays. Thirty-five of the DWI+ lesions (97.2%) were ipsilateral and one lesion was contralateral (2.8%). The mean number of lesions was 5.9±6.4 in patients tested for P2Y12 response compared with 3.6±3.9 in the other group. Regardless of institution, ischemic lesions were significantly more frequent in patients older than 60 years than in younger patients ($p=0.038$). No significant association was found between aneurysm size, aneurysm location, and number of implanted devices.

DISCUSSION

Silent ischemic brain lesions after endovascular procedures remain a relatively common event despite increased experience with endovascular techniques and routine use of anticoagulant and antiplatelet drugs. The clinical significance and long-term effects of these events, however, is controversial and a matter of debate. With recent advancements in endovascular technology, especially with widespread use of flow diverters, it is opportune to investigate the rate of ischemic events following PED therapy, and potential risk factors for thromboembolic events.

The PED is a cylindrical tightly braided mesh composed of 48 individual multi-alloy microfilaments. One of the unique characteristics of the PED and flow diverters, in general, is a high metal surface area coverage when fully deployed inside the parent vessel. The higher metal density promotes vessel remodeling and acts as a scaffold for neo-endothelialization while maintaining blood flow to covered perforating branches. At the same time it creates the potential for increased thrombogenicity compared with other endovascular techniques.

Our prospective study showed an incidence of 62.7% of DWI+ events on postprocedure MRI with 8.1% of patients with DWI+ lesions demonstrating neurological symptoms. Both rates found in this study compared favorably with previous endovascular techniques. Hahnemann *et al*[7] used a similar protocol to investigate the rate of ischemic events after stent-assisted coiling in 75 patients and reported an incidence of 64% of DWI+ lesions and 6.7% rate of neurological morbidity, with 1.3% of permanent deficits.[7] In other studies investigating aneurysm coiling alone, the incidence of silent DWI+ lesions ranged from 10% in earlier studies to 71% in larger series.[8–10] Schubert *et al*[11] compared the rate of ischemic events in patients treated with stent-assisted coiling versus conventional coiling and found no difference between the two procedures, whereas Altay *et al*[12] examined a heterogeneous population of ruptured and unruptured aneurysms using coiling, stent-assisted coiling, and balloon-assisted coiling. Using a similar DWI protocol, the study found no significant difference in ischemic events between each embolization technique and demonstrated that ruptured aneurysms have a higher incidence of thromboembolic events regardless of technique. These results and our findings seem to

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show that using stents or flow diverters for treatment of aneurysms does not significantly increase the risk of silent embolic events compared with conventional coiling. This seems counterintuitive since these devices add foreign material inside the vessel and also have technical complexity and require increased procedure time, but it also shows that the risk factors and fundamental basis for thromboembolism during endovascular interventions are not well understood.

In this study the only identified risk factor for a higher rate of DWI+ events was older age (≥60 years). Is it intuitive that older patients are more likely to have a diffuse atherosclerotic burden, and catheter navigation may result in plaque dislodgment and distal emboli. In addition, this finding is well supported by previous studies of endovascular intervention, including aneurysm embolization[7] and diagnostic angiography.[13] In one of the few studies assessing the rate of ischemic events after flow diverter treatment, Iosif *et al*[14] found an incidence of 81.6% of silent DWI+ lesions in a cohort of 38 patients treated with PED. The authors could not establish a correlation between DWI+ events and aneurysm location, clinical complications, or scores on the modified Rankin Scale at 3 months. Similarly, we could not establish a correlation between the number of devices deployed and silent ischemic events and our analysis of clinical events did not continue after hospital discharge. However, in our patient cohort the majority of patients received a single device and that might have weakened our ability to identify a correlation.

In contrast, in the study performed by Tan *et al*,[15] the authors identified deployment of multiple PEDs as a risk factor for symptomatic ischemic events but could not establish a correlation between multiple devices and silent DWI+ events. The degree of metal surface area coverage provided by one device typically ranges from 30% to 35% when fully deployed and opposed to the vessel wall. By overlapping multiple devices, operators can manipulate the degree of metal coverage obtained, which equates to more thrombogenic surface for platelet aggregation and increased risk of perforator occlusion. Interestingly, the only risk factor for DWI changes after PED placement found by Tan *et al* was female gender and the authors hypothesized that a combination of hormonal therapy, menopause, and gender differences in inflammatory and platelet aggregation biomarkers may contribute to this phenomenon. The incidence of DWI+ events (50.9%) and neurological complications (6.8%) in their patient cohort (n=74) was similar to the rate found in our study and further supports the premise that the safety of PED therapy for ischemic events is comparable to that of previous endovascular techniques. Of note, intraparenchymal hemorrhages following PED therapy are a well-described phenomenon and may be explained by silent ischemic events and increased ischemic burden since these lesions may undergo hemorrhagic transformation in the presence of heparin and dual antiplatelet agents. The occurrence of hemorrhagic events contralateral to the intervention further supports this theory.

Routine use of platelet function tests in the neurovascular community continues to be debated. The cardiac literature has provided evidence from multiple prospective randomized studies that individually tailored antiplatelet therapy based on point-of-care platelet function assays results in a decreased rate of major cardiovascular events after coronary stenting.[16 17] However, these tests have not been widely adopted in neurovascular centers and there is no consensus on the target preprocedure values and dual antiplatelet management. Likewise, there were considerable differences in the testing protocol between the two participating hospitals on our study. Although a lower rate of ischemic events was seen in patients when platelet function was measured and ticagrelor was used (60% vs 71.4%), our overall results showed that routine testing for aspirin and clopidogrel response before intervention did not have a statistically significant correlation with postoperative ischemic events. Tan *et al*[15] also attempted to establish a relationship between preprocedural response to antiplatelet therapy on VerifyNow and rate of ischemic events and their results support our findings. To our knowledge, only one study has identified response on platelet function assays as an independent predictor of perioperative complications after treatment with PED.[18] The authors used a similar cut-off point to identify clopidogrel hyporesponders (>240 PRU) but, in contrast to our study, the neurological events reported occurred up to 6 months after discharge and included a high rate of symptomatic thromboembolic events (12.5%). Based on the recent IntrePED study (International Retrospective Study of Pipeline Embolization Device), involving 793 patients and 906 aneurysms, the risk of ischemic strokes after PED is approximately 4.7%.[3] However, a limitation of our analysis was that only 24% of the patient cohort was treated without prior assessment of platelet function, which might have skewed the data. In addition, even though more studies are needed to determine the role of platelet function assays in neurovascular procedures, from our clinical experience we believe that when using flow diverters, checking the preoperative PRU values and switching clopidogrel to other inhibitors of the P2Y12 receptor in hyporesponders is a safe strategy and may contribute to a lower rate of thromboembolic events.

Study limitations

Given that this study reflects the experience of two institutions, potential confounding factors and inherent biases might be introduced into the dataset before our analysis. The relatively modest sample size might also have undermined the power of the study and our ability to identify differences between two groups. Finally, because we did not carry out DWI before interventions we cannot eliminate the possibility that some of the DWI lesions might have been caused by other events, such as diagnostic angiography (performed in seven patients).

CONCLUSIONS

Silent DWI+ events after treatment of intracranial aneurysms with PED were identified in 62.7% of patients, with 8.1% demonstrating neurological symptoms. We identified older age (>60 years) as the only risk factor for silent ischemic lesions on MRI. Based on our findings, treatment of intracranial aneurysms with flow diverters has a low risk of neurological morbidity and does not lead to more thromboembolic events than with stent-assisted and conventional coiling.

Contributors All authors contributed to production and revision of this article, and gave their final approval for its submission to this journal.

Competing interests RH is a consultant for Covidien, Stryker, and Codman.

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