Risk Factors for Ischemic Complications following Pipeline Embolization Device Treatment of Intracranial Aneurysms: Results from the IntrePED Study

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ABSTRACT

BACKGROUND AND PURPOSE: Risk factors for acute ischemic stroke following flow-diverter treatment of intracranial aneurysms are poorly understood. Using the International Retrospective Study of Pipeline Embolization Device (IntrePED) registry, we studied demographic, aneurysm, and procedural characteristics associated with postoperative acute ischemic stroke following Pipeline Embolization Device (PED) treatment.

MATERIALS AND METHODS: We identified patients in the IntrePED registry with post-PED-treatment acute ischemic stroke. The rate of postoperative acute ischemic stroke was determined by demographics, comorbidities, aneurysm characteristics, and procedure characteristics (including anticoagulation use, platelet testing, number of devices used, sheaths, and so forth). Categoric variables were compared with χ^2 testing, and continuous variables were compared with the Student *t* test. Odds ratios and 95% confidence intervals were obtained by using univariate logistic regression. Multivariate logistic regression analysis was used to determine which factors were independently associated with postoperative stroke.

RESULTS: Of 793 patients with 906 aneurysms, 36 (4.5%) patients had acute ischemic stroke. Twenty-six (72.2%) strokes occurred within 30 days of treatment (median, 3.5 days; range, 0–397 days). Ten patients died, and the remaining 26 had major neurologic morbidity. Variables associated with higher odds of acute ischemic stroke on univariate analysis included male sex, hypertension, treatment of MCA aneurysms, treatment of fusiform aneurysms, treatment of giant aneurysms, and use of multiple PEDs. However, on multivariate analysis, the only one of these variables independently associated with stroke was treatment of fusiform aneurysms (OR, 2.74; 95% CI, 1.11–6.75; $P = .03$). Fusiform aneurysms that were associated with stroke were significantly larger than those not associated with stroke (mean, 24.5 ± 12.5 mm versus 13.6 ± 6.8 mm; $P < .001$).

CONCLUSIONS: Ischemic stroke following PED treatment is an uncommon-but-devastating complication. Fusiform aneurysms were the only variable independently associated with postoperative stroke.

ABBREVIATIONS: PED = Pipeline Embolization Device; IntrePED = International Retrospective Study of Pipeline Embolization Device

The Pipeline Embolization Device (PED; Covidien, Irvine, California) is increasingly used in the treatment of intracranial aneurysms.[1-5] The bare metal construct of the PED serves as a scaffold for neointimal proliferation, thereby excluding the aneurysm sac from the parent artery.[6,7] A number of previous studies have demonstrated that the PED is associated with high rates of aneurysm occlusion with relatively low complication rates.[1,3] Although uncommon, postoperative acute ischemic stroke is the most common neurologic complication to occur following treatment of aneurysms with flow diverters such as the PED, with estimated rates of 3%–6% of patients.[3,8,9] Understanding the risk factors for post-Pipeline ischemic complications is important for risk stratification and consent of these patients. Using the International Retrospective Study of Pipeline Embolization Device

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registry (IntrePED), we compared the clinical and procedural characteristics of patients who had postoperative acute ischemic stroke with those who did not, to determine which clinical and procedural characteristics were associated with this condition.

MATERIALS AND METHODS

Study Design and Participants

This study is a subanalysis of the IntrePED study, which has been previously published.[9] Details regarding ethics committee and institutional review board approval and inclusion and exclusion criteria are provided in the original article.[9] Several additional subgroup analyses separate from this study are currently underway using data from the IntrePED registry. This study will be the only subgroup analysis performed examining variables associated with acute ischemic stroke in the IntrePED registry. We retrospectively evaluated all patients with intracranial aneurysms treated with the Pipeline Embolization Device in the IntrePED registry. Seven hundred ninety-three patients with 906 treated aneurysms were enrolled.

Procedures

Because this was a retrospective registry, procedural details and patient management varied across centers. All centers reported baseline characteristics of patients and aneurysms, procedural information, and follow-up information from clinic visits or telephone calls by using a common study protocol form. Site investigators identified patients with acute ischemic stroke by using the study protocol form. All complications, including acute ischemic stroke, were reviewed in detail by an Adverse Events Review Committee, comprising 3 members of the Steering Committee, including the overall study principal investigator. The committee determined whether the acute ischemic stroke was major or minor. A "major" adverse event was defined as an ongoing clinical deficit at 7 days following the event. All major adverse events are included in the neurologic morbidity and mortality rates. Timing of all adverse events was in relation to the time of PED placement.

Baseline Characteristics and Outcomes

For each patient, the following characteristics were collected as part of this study: age, sex, hypertension, control of hypertension, smoking status, aneurysm location, aneurysm rupture status, aneurysm type, aneurysm size, use of antiplatelet medications before the procedure, use of platelet aggregation studies, heparin administration and reversal, number of PEDs used, type of sheath used, type of guide catheter used, type of microcatheter used, type of guidewire used, balloons used, and type of closure device used. The incidence of acute ischemic stroke was calculated for each of the above-mentioned variables.

In addition, for patients with any acute ischemic stroke, we obtained the following information: whether the stroke was ipsilateral or contralateral to the device, timing after the operation, and final clinical outcome (minor morbidity, major morbidity, or death). "Minor morbidity" was defined as a clinical deficit that persisted for <7 days, and "major morbidity" was defined as a clinical deficit that persisted ≥7 days.

Statistical Analysis

Statistical analyses were performed by using SAS, Version 9.2 (SAS Institute, Cary, North Carolina). Descriptive statistics were used to present the data and to summarize the results. Discrete variables are presented by using frequency distributions and cross-tabulations. Continuous variables are summarized by presenting the number of observations, mean, and SD and median, minimum, and maximum values. For categoric variables, differences between the groups were tested by using appropriate contingency table analyses (exact or χ^2 approximations). For continuous variables, the differences were tested by using an unpaired Student t test or a nonparametric test, depending on variable distribution. Odds ratios and 95% confidence intervals were obtained by using univariate logistic regression. We also performed a multivariate logistic regression analysis to determine which factors were independently associated with postoperative stroke. Variables included in this model were those that were statistically significantly associated with postoperative stroke on the univariate analysis. Because treatment of fusiform aneurysms was the only variable significantly associated with postoperative stroke on the multivariate analysis, we performed a separate post hoc subgroup analysis comparing the features of fusiform aneurysms that were and were not associated with stroke. All statistical analyses were performed on a per-patient basis.

Role of the Funding Source

The principal investigator and steering committee were independent of the funding source (Medtronic; Dublin, Ireland). The steering committee interpreted the results, and the principal investigator wrote the report. The study sponsor was responsible for site management, data management, statistical analysis, and safety reporting. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

RESULTS

Patient and Aneurysm Characteristics and Acute Ischemic Stroke

A summary of the baseline characteristics of all patients included in the IntrePED registry is provided elsewhere.[9] Thirty-six (4.5%) patients had postoperative acute ischemic stroke, while 757 patients (95.5%) did not. There was no difference in the mean age of patients with and without acute ischemic stroke (54.2 ± 15.6 years versus 57.0 ± 14.1 years, $P = .2516$); 8.1% of male patients (13/161) and 3.6% of female patients (23/632) had acute ischemic stroke ($P = .02$). Hypertension was also associated with postoperative stroke because 9.2% of patients with hypertension (23/249) and 3.8% of patients without hypertension (12/318) had stroke ($P = .009$). These data are summarized in Table 1.

There was no difference in the rate of acute ischemic stroke between anterior circulation aneurysms (30/704, 4.3%) and posterior circulation aneurysms (6/89, 6.7%) ($P = .29$). Patients with middle cerebral artery aneurysms had higher odds of stroke than those with internal carotid artery aneurysms (12.5%, 5/40 versus 3.9%, 23/590; $P = .01$). The rate of stroke (9.3%, 4/43) in patients

Table 1: Demographic and aneurysm characteristics

Variable	No. Stroke/No. Total (%)	OR (95% CI)	*P* Value
Age (yr)	54.2 ± 15.6/57.0 ± 14.1	0.99 (0.97–1.01)	.2516
Sex			
Male	8.1% (13/161)	2.33 (1.15–4.70)	.0187
Female	3.6% (23/632)	Ref	
Hypertension			
Yes	9.2% (23/249)	2.60 (1.26–5.33)	.0093
No	3.8% (12/318)	Ref	
Controlled hypertension			
Yes	8.7% (18/206)	3.03 (1.54–5.94)	.0013
No	0.0% (0/4)	Ref	
Current smoker			
Yes	4.3% (4/94)	0.93 (0.32–2.68)	.8878
No	4.6% (32/699)	Ref	
Aneurysm location			
Posterior circulation	6.7% (6/89)	1.62 (0.66–4.02)	.2940
Anterior circulation	4.3% (30/704)	Ref	
Aneurysm location by vessel			
Internal carotid artery	3.9% (23/590)	Ref	
Anterior cerebral artery	12.5% (1/8)	4.83 (0.72–32.44)	.1052
Basilar artery	9.3% (4/43)	2.75 (0.94–8.02)	.0636
Middle cerebral artery	12.5% (5/40)	3.74 (1.38–10.16)	.0096
PcomA	1.9% (1/53)	0.69 (0.13–3.74)	.6668
Vertebral artery	6.1% (2/33)	1.92 (0.49–7.55)	.3523
Other	0.0% (0/26)	0.46 (0.03–8.12)	.5928
Rupture status			
Ruptured	5.4% (4/74)	1.23 (0.42–3.57)	.7074
Unruptured	4.5% (32/719)	Ref	
Aneurysm type			
Saccular	3.2% (19/600)	Ref	
Fusiform	12.7% (13/102)	4.47 (2.13–9.36)	.0001
Dissecting	3.8% (2/53)	1.20 (0.27–5.29)	.8105
Other	5.3% (2/38)	1.70 (0.38–7.58)	.4873
Aneurysm size			
<10 mm	2.6% (10/387)	Ref	
10–24.9 mm	4.7% (16/338)	1.87 (0.84–4.19)	.1260
≥25 mm	14.3% (9/63)	6.28 (2.44–16.16)	.0001

Note:—Ref. indicates reference; PcomA, posterior communicating artery.

Table 2: Multivariate analysis

Variable	OR (95% CI)	*P* Value
Male	1.21 (0.51–2.85)	.6636
HTN	2.01 (0.99–4.08)	.0533
ACA vs ICA	4.47 (0.58–34.44)	.1502
BAS vs ICA	1.12 (0.31–4.04)	.8584
MCA vs ICA	2.79 (0.91–8.60)	.0734
Other artery vs ICA	0.53 (0.03–9.04)	.6596
PcomA vs ICA	0.84 (0.15–4.53)	.8351
Vertebral artery vs ICA	1.27 (0.27–6.09)	.7620
Dissecting vs saccular	0.83 (0.19–3.63)	.8089
Fusiform vs saccular	2.74 (1.11–6.75)	.0283
Other aneurysm type vs saccular	1.71 (0.44–6.66)	.4370
Aneurysm size	1.03 (0.99–1.07)	.1370
PED No.	1.17 (0.94–1.45)	.1610

Note:—HTN indicates hypertension; ACA, anterior cerebral artery; BAS, basilar artery; PcomA, posterior communicating artery.

with basilar artery aneurysms was higher than in those with internal carotid artery aneurysms, but the difference trended toward statistical significance ($P = .06$). There was no difference in stroke rates between ruptured (5.4%, 4/74) and unruptured (4.5%, 32/719) aneurysms ($P = .71$). Patients with fusiform aneurysms had significantly higher stroke rates (12.7%, 13/102) than those with saccular aneurysms (3.2%, 19/600; $P = .0001$). Giant aneurysms had higher rates of stroke than small aneurysms (14.3%, 9/63 versus 2.6%, 10/387; $P = .0001$). These data are summarized in Table 1.

Treatment Characteristics and Acute Stroke

The stroke rate in patients with 1 PED was 3.0% (16/533) compared with 7.1% (13/183) in patients with 2 PEDs ($P = .02$) and 9.2% (7/76) in patients with ≥3 PEDs ($P = .008$). There was no difference in stroke rates based on how PEDs were used. Use of a microcathether other than the Marksman (Covidien) was associated with a 16.7% risk of stroke (4/24), while the use of a Marksman was associated with a 5.7% risk of stroke (32/557, $P = .04$). There was no difference in stroke rates between patients with and without preprocedural antiplatelet therapy (4.6%, 31/681 versus 4.5%, 5/112; $P = .97$) or among patients with and without preprocedural platelet aggregation studies (5.1%, 29/564 versus 3.1%, 7/229, $P = .21$). These data are summarized in the On-line Table.

Multivariate Analysis

On multivariate analysis, the only variable independently associated with postoperative stroke was treatment of fusiform aneurysms (OR, 2.74; 95% CI, 1.11–6.75, $P = .03$). Higher rates of acute stroke were observed in patients with hypertension (OR, 2.01; 95% CI, 0.99–4.08; $P = .053$) and in patients with aneurysms of the MCA (OR, 2.79; 95% CI, 0.91–8.60; $P = .07$), but the differences were not statistically significant. The use of multiple PEDs was not independently associated with postoperative infarct (OR, 1.17; 95% CI, 0.94–1.45; $P = .16$). These data are summarized in Table 2.

Timing and Clinical Outcomes of Stroke

Of the 36 patients with stroke, 21 (58.3%) had stroke within 1 week of the procedure. Five patients (13.9%) had stroke between 1 week and 1 month of the procedure, 5 patients (13.9%) had stroke between 1 and 6 months after the procedure, and 5 patients had stroke ≥6 months after the procedure (13.9%). The median time of onset for stroke was 3.5 days, and the mode was 0 days as 8 patients had stroke on day 0. Among patients with stroke, 10 (27.0%) died and 26 (73.0%) had major neurologic morbidity. The location of the stroke was ipsilateral to the device in 34 of 36 patients (94.4%), including 2 patients who also had contralateral infarcts. In 2 patients, the infarcted area was located contralateral to the device and there was no ipsilateral infarct. None of the strokes occurred in the intraoperative period.

Table 3: Subgroup analysis of fusiform aneurysms

Aneurysm Characteristics	With Stroke	Without Stroke	*P* Value
Aneurysm size (mm)			<.001
Mean (No.)	24.5 ± 12.5 (12)	13.6 ± 6.8 (88)	
Median (range)	21.0 (13.0–55.0)	11.8, (1.6–42.0)	
Aneurysm neck (mm)			.010
Mean (No.)	26.2 ± 19.5 (9)	10.2 ± 5.2 (60)	
Median (range)	22.0 (8.0–53.0)	9.0 (2.0–27.0)	
Aneurysm location			.211
Posterior circulation	38.5% (5/13)	22.5% (20/89)	
Anterior circulation	61.5% (8/13)	77.5% (69/89)	
Aneurysm location by vessel			.677
ICA	53.8% (7/13)	59.6% (53/89)	
ACA	0.0% (0/13)	1.1% (1/89)	
BA	23.1% (3/13)	10.1% (9/89)	
MCA	7.7% (1/13)	13.5% (12/89)	
PcomA	0.0% (0/13)	0.0% (0/89)	
VA	15.4% (2/13)	10.1% (9/89)	
Other	0.0% (0/13)	5.6% (5/89)	
Presented with ruptured aneurysm	0.0% (0/13)	5.6% (5/89)	.381

Note:—BA indicates basilar artery; VA, vertebral artery; PcomA, posterior communicating artery; ACA, anterior cerebral artery.

Subgroup Analysis of Fusiform Aneurysms

On the subgroup analysis of fusiform aneurysms, 13 fusiform aneurysms were included in the stroke group and 89 were included in the nonstroke group. Fusiform aneurysms associated with stroke were significantly larger than those not associated with stroke (mean, 24.5 ± 12.5 mm versus 13.6 ± 6.8 mm; $P <$ .001). Aneurysm neck size was also significantly larger in the stroke subgroup than in the nonstroke subgroup (mean, 26.2 ± 19.5 mm versus 10.2 ± 5.2 mm; $P = .01$). There was no difference in aneurysm location or rupture status between groups. These data are summarized in Table 3.

DISCUSSION

Our current large, multicenter study of flow-diversion therapy demonstrated that approximately 5% of patients have postoperative acute ischemic stroke with most occurring in the early postoperative period. All patients who experienced postoperative acute ischemic stroke in our study either had major morbidity or died. In our series, treatment variables associated with stroke included male sex, hypertension, treatment of MCA aneurysms, giant aneurysms, fusiform aneurysms, and the use of multiple PEDs. However, treatment of fusiform aneurysms was the only variable independently associated with postoperative stroke. Most interesting, fusiform aneurysms made up more than one-third of all cases of postoperative stroke, while comprising slightly more than one-tenth of all patients with PED. Fusiform aneurysms associated with stroke were generally large or giant with a mean size of nearly 25 mm and a mean neck size of 26 mm. These findings are important because they provide additional information that can be used to risk-stratify patients treated with the PED by using a multi-institutional real-world data base.

The stroke rate in IntrePED is similar to that in other large studies. In one meta-analysis, Brinjikji et al[3] noted an acute ischemic stroke rate of 5.0% within 30 days of flow-diverter treatment and 3.0% beyond 30 days. These findings are similar to those of our study in which we found that nearly 75% of acute ischemic stroke events occurred within 30 days of the procedure. Ischemic stroke rates in a more recently published meta-analysis on aneurysm treatment with flow diverters found an ischemic stroke rate of 4.1%, similar to that seen in our study.[10] In the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial, the rate of acute ischemic stroke within 180 days of treatment was 6.5%, with 2.8% of patients having stroke secondary to in-stent thrombosis or occlusion caused by in-stent stenosis.[8] The rate of stroke after 6 months in PUFS was 0%, while in our study, the stroke rate after 6 months was just 0.6% (5/793).[8]

There are a number of potential mechanisms for postoperative cerebral infarction following PED therapy. Perioperative stroke secondary to catheter-related thromboemboli is a common mechanism of stroke in this population as many studies have now demonstrated that well over 50% of patients treated with flow diverters have multiple foci of restricted diffusion on immediate postoperative MR imaging.[11] Acute and subacute in-stent thrombosis during the procedure and in the postoperative period resulting in occlusion of the parent vessel with or without distal emboli is another common mechanism of stroke, possibly related to the thrombogenic nature of the bare metal construct or lack of adequate antiplatelet therapy.[12,13] Other mechanisms of stroke include particle emboli from devices such as catheters or sheaths.[14-16] Intraoperatively, acute thrombus formation can be mitigated by prompt injection of glycoprotein IIb/IIIa platelet inhibitors; however, it is difficult to reduce the long-term risk of thromboembolic events associated with flow-diverter treatment.[3,9] In general, delayed ischemic events are uncommon.[17]

In our series, higher stroke rates were seen following treatment of MCA and basilar artery aneurysms than in ICA aneurysms, though these results are not statistically significant. Prior studies have demonstrated that aneurysms of the posterior circulation and MCA are at higher risk of thromboembolic complications due to the risk of perforator infarction.[3,18] Perforator infarction due to coverage of the lenticulostriates and brain stem perforators secondary to reduced flow and perforator occlusion are likely responsible for the higher stroke rates seen in these patients in some studies.[18,19] In a study of 17 patients with flow-diverter coverage of perforator arteries, Gawlitza et al[18] noted that 7 of 17 patients had infarctions in the territory of the covered perforators, of which 2 were symptomatic. In their meta-analysis of >1300 cases, Brinjikji et al[3] noted a perforator infarction rate of 3.0% among all treated aneurysms with a significantly higher rate of perforator infarction in the treatment of posterior circulation aneurysms than in anterior circulation aneurysms.

A number of studies have reported poor outcomes and high rates of thrombosis in the treatment of dolichoectatic and fusiform aneurysms, particularly of the posterior circulation, with flow diverters in general.[9,20,21] High rates of infarction

seen in these patients are likely due to a combination of poor wall apposition due to the large size of the aneurysm, early discontinuation of antiplatelet therapy, and the requirement for multiple PEDs.[20,21] Recently, there has been increased interest in the relationship between wall apposition of the flow diverter and rates of delayed postoperative stroke.[22] It is thought that poor wall apposition can result in delayed endothelialization of the stent, resulting in an increased risk of in-stent thrombosis in the delayed postoperative period.[20,21] This is supported by the fact that the fusiform aneurysms that were associated with stroke in our series were generally large or giant, with a mean aneurysm size of nearly 25 mm and a mean neck size of 26 mm. The large aneurysm maximum diameter and neck size likely made achieving good wall apposition, thus increasing the risk of in-stent thrombosis. As a means to mitigate the risk of delayed thromboembolic events in the treatment of fusiform aneurysms secondary to delayed endothelialization, some authors have advocated the use of prolonged dual-antiplatelet therapy.[21] However, the efficacy of such regimens needs to be studied systematically.

Limitations

Our study has limitations. First, the interpretation of outcomes in this study should be viewed with caution because the study was not randomized, did not include an active comparator group, or was not powered to demonstrate a significant association of postoperative ischemic stroke with any of the variables studied. The study protocol did not require regular postoperative CT or MR imaging, and there were variable lengths of patient follow-up. Thus, we cannot determine the rate of silent ischemia in these patients, and it is possible that patients who had strokes in the delayed postoperative period were not included due to incomplete follow-up. Patients were not censored early before ascertainment of the primary outcome. Another limitation is that for patients undergoing platelet testing, we do not have information regarding platelet responsiveness before the ischemic event or whether and how antiplatelet prescriptions changed in response to these tests. Adverse events were self-reported in this study, and there is a general tendency toward underestimation of adverse events when they are self-reported. Last, we do not have any consistent data regarding how these strokes were managed.

CONCLUSIONS

In conclusion, acute ischemic stroke following endovascular treatment of intracranial aneurysms with the PED is an uncommon-but-devastating complication, with 100% of patients having major morbidity or mortality. Several patient and procedural characteristics as well as aneurysm shape, size, and location appear to be associated with postoperative ischemic stroke after PED treatment. Fusiform aneurysms were the only variable independently associated in the multivariate analysis. Most strokes occurred within 1 month of the procedure, and delayed ischemic events were rare.

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