Pipeline Embolization Device with or without Adjunctive Coil Embolization: Analysis of Complications from the IntrePED Registry


*AJNR Am J Neuroradiol* 2016, 37 (6) 1127-1131
doi: https://doi.org/10.3174/ajnr.A4678
http://www.ajnr.org/content/37/6/1127
Pipeline Embolization Device with or without Adjunctive Coil Embolization: Analysis of Complications from the IntrePED Registry


ABSTRACT

SUMMARY: Flow diversion to treat cerebral aneurysms has revolutionized neurointerventional surgery. Because the addition of coils potentially increases the time and complexity of endovascular procedures, we sought to determine whether adjunctive coil use is associated with an increase in complications. Patients in the International Retrospective Study of Pipeline Embolization Device registry were divided into those treated with the Pipeline Embolization Device alone (n = 689 patients; n = 797 aneurysms; mean aneurysm size, 10.3 ± 7.6 mm) versus those treated with the Pipeline Embolization Device and concurrent coil embolization (n = 104 patients; n = 109 aneurysms; mean aneurysm size, 13.6 ± 7.8 mm). Patient demographics and aneurysm characteristics were examined. Rates of neurologic morbidity and mortality were compared between groups. The Pipeline Embolization Device with versus without coiling required a significantly longer procedure time (135.8 ± 63.9 versus 96.7 ± 46.2 min; P < .0001) and resulted in higher neurological morbidity (12.5% versus 7.8%; P = .03). These data suggest that either strategy represents an acceptable risk profile in the treatment of complex cerebral aneurysms and warrants further investigation.

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

The recent development of flow diversion for cerebral aneurysms that are difficult to treat has ushered in an exciting time in the world of neurointerventional surgery.1-12 Reports in the literature, however, are conflicting concerning the optimal strategy in using this new device.1,2,4,13,16,18-21 The addition of coil embolization to flow diversion, while prevalent in daily use, has not been subjected to a large systematic analysis.7-11,16,21-24 The earliest case report hypothesized that coils within the aneurysm sac can augment the degree of flow diversion with the goal of improved occlusion of the aneurysm.1 Others believe that adjunctive coil embolization does little to improve the already high occlusion rates obtained by using the Pipeline Embolization Device (PED; Covidien, Irvine, California) alone.21 Furthermore, there have been reports of complications associated with overly dense coil embolization of aneurysms in this setting.22

We analyzed the International Retrospective Study of Pipeline Embolization Device (IntrePED [ClinicalTrials.gov identifier: NCT01558102]) data to determine whether there was an increase in neurologic complications associated with the use of the PED and adjunctive coil embolization.

MATERIALS AND METHODS

This study is a subanalysis of IntrePED registry data obtained from a multicenter, observational, international registry of patients treated with the PED. The primary objective of IntrePED was to identify any neurologic events following treatment with the PED. The IntrePED registry includes patients treated with the PED starting in July 2008 and concluding in July 2013, following the enrollment of 793 patients. Because the study was conducted retrospectively, the protocol did not specify the coiling methodology, and the decision to use coils with the PED was left to the discretion of the treating physician. Details regarding the institutional review board and ethics committee approvals, patient population, and protocol requirements are described in the primary IntrePED article.17

This subanalysis was performed to compare the safety outcomes of patients treated with the PED alone (PED group) with those of patients treated with the PED and adjunctive coil embolization (PED/coil group). Data collected for analysis were basic
demographic information, including patient age, sex, and history of aneurysm rupture; aneurysm characteristics, including aneurysm size, neck size, shape, and location; procedural data, including procedure time and devices used; and follow-up data, including any complications. The primary outcomes were neurologic mortality and combined neurologic morbidity and mortality. Neurologic morbidity was predefined as the composite of the following neurologic complications: spontaneous aneurysm rupture, ipsilateral intracranial hemorrhage, ischemic stroke, parent artery stenosis, and cranial neuropathy. These complications were characterized as major or minor, with “major” defined as an ongoing clinical deficit at 7 days after the event. All major adverse events are included in the neurologic morbidity and mortality rates.

The data were analyzed to determine whether there were any significant differences between those patients treated with the PED alone versus those treated with the PED and adjunctive coils. Differences in continuous variables between the 2 groups were tested by using the Wilcoxon rank sum test. Differences in categorical variables between groups were analyzed by using the chi-square or Fisher exact test. Data are presented as the number of events and percentages for categoric variables between groups were calculated with chi-square tests. Values for sex were calculated with the chi-square test.

Table 1: Patient details

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>PED/Coils</th>
<th>PED Alone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of aneurysms</td>
<td>109 (12.0%)</td>
<td>797 (88.0%)</td>
<td></td>
</tr>
<tr>
<td>No. (%) of patients</td>
<td>104 (13.1%)</td>
<td>689 (86.9%)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td><em>279</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>57.6 ± 15.1</td>
<td>56.8 ± 14.0</td>
<td></td>
</tr>
<tr>
<td>Median, range</td>
<td>61.5; 3–81</td>
<td>57; 9–86</td>
<td></td>
</tr>
<tr>
<td>Sex (No., %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (23.1%)</td>
<td>137 (19.9%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>80 (76.9%)</td>
<td>552 (80.1%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td><em>7.18</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>21.1 ± 8.8</td>
<td>22.1 ± 8.8</td>
<td></td>
</tr>
<tr>
<td>Median, range</td>
<td>20.8; 0.1–45.0</td>
<td>21.0; 0.1–60.5</td>
<td></td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>135.8 ± 63.9</td>
<td>96.7 ± 46.2</td>
<td></td>
</tr>
<tr>
<td>Median, range</td>
<td>120; 46–365</td>
<td>87; 10–376</td>
<td></td>
</tr>
</tbody>
</table>

*P values for age, duration of follow-up, and procedure time were calculated with Wilcoxon rank sum tests. P value for sex was calculated with the chi-square test.

Table 2: Aneurysm characteristics

<table>
<thead>
<tr>
<th>Aneurysm Characteristics</th>
<th>PED/Coils</th>
<th>PED Alone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of aneurysms</td>
<td>109</td>
<td>797</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>104</td>
<td>689</td>
<td></td>
</tr>
<tr>
<td>Aneurysm size (mm)a</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean</td>
<td>13.6 ± 7.8</td>
<td>10.3 ± 7.6</td>
<td></td>
</tr>
<tr>
<td>Median, range</td>
<td>12; 1.6–45.0</td>
<td>8; 1.0–55.0</td>
<td></td>
</tr>
<tr>
<td>Aneurysm neck (mm)</td>
<td></td>
<td></td>
<td>.17</td>
</tr>
<tr>
<td>Mean</td>
<td>6.4 ± 3.0</td>
<td>6.2 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Median, range</td>
<td>6; 0.8–16.0</td>
<td>5; 0.9–53.0</td>
<td></td>
</tr>
<tr>
<td>Aneurysm shape (No., %)</td>
<td></td>
<td></td>
<td>.366</td>
</tr>
<tr>
<td>Fusiform</td>
<td>13 (11.9%)</td>
<td>103 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Saccular</td>
<td>85 (78.0%)</td>
<td>604 (75.8%)</td>
<td></td>
</tr>
<tr>
<td>Dissecting</td>
<td>3 (2.8%)</td>
<td>51 (6.4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (7.3%)</td>
<td>39 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm location (%)</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>70 (64.2%)</td>
<td>614 (77.0%)</td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>8 (7.3%)</td>
<td>35 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>0 (0%)</td>
<td>15 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Basilar artery</td>
<td>16 (14.7%)</td>
<td>28 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15 (13.8%)</td>
<td>105 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm ruptured at initial presentation (%)</td>
<td>13 (11.9%)</td>
<td>63 (7.9%)</td>
<td>.155</td>
</tr>
<tr>
<td>Multiple PEDs used (%)</td>
<td>34 (31.2%)</td>
<td>274 (34.5%)</td>
<td>.499</td>
</tr>
</tbody>
</table>

*P values for aneurysm size and neck size were calculated with Wilcoxon rank sum tests. P values for categoric variables were calculated with chi-square tests.

RESULTS

The registry included 793 patients with 906 aneurysms: 689 patients with 797 aneurysms were treated with the PED alone, and 104 patients with 109 aneurysms were treated with PED/coil (Table 1). While the patient ages, sex, and length of follow-up were well matched, procedure times were significantly increased for the PED/coil cohort compared with the PED alone group (135.8 ± 63.9 minutes versus 96.7 ± 46.2 minutes, P < .0001).

The mean aneurysm and neck sizes were statistically larger in the PED/coil cohort than in the PED alone group (aneurysm size, 13.6 ± 7.8 mm versus 10.3 ± 7.6 mm, P < .0001; neck size, 6.4 ± 3.0 mm versus 6.2 ± 5.1 mm, P = .017) (Table 2). These larger aneurysms were also more likely to require multiple PEDs during treatment (Table 3). There was also a statistically significant difference in the location of aneurysms treated between the 2 groups (P < .0001). There were significantly fewer internal carotid artery aneurysms treated in the PED/coil cohort compared with the PED alone group (64.2% versus 77%, P = .006). There were significantly more basilar artery aneurysms treated by PED/coil compared with PED alone (14.7% versus 3.5%, P < .0001). There was no statistically significant difference in presentation with subarachnoid hemorrhage between the 2 groups (PED/coil 11.9% versus PED alone 7.9%, P = .155).

Overall, 13 of 104 (12.5%) patients in the PED/coil cohort experienced a major neurologic complication and/or mortality versus 54 of 689 (7.8%) patients in the PED alone cohort (P = .13) (Table 4). Neither the overall nor the individual complication rates reached statistical significance.

DISCUSSION

While the use of adjunctive coil embolization with the PED is not novel, there are questions regarding the efficacy of, and the potential for, increased complications with this strategy compared with PED embolization alone. Certain authors have advocated coil embolization as a method of improving occlusion rates and minimizing the potential for catastrophic aneurysm rupture following the use of flow-diverting stents.23,25,26 Others have argued that the addition of coil embolization to the procedure yields no significant added advantage in regard to treatment efficacy.21 However, our single-center results, which have been previously presented, did identify a statistically significant increase in the need for retreatment with a strategy of PED alone versus PED/coil.27
Additionally, we previously reported our overall (31.7%) and permanent complication (3.2%) rates following use of the PED.\textsuperscript{19} However, we did not examine any potential differences in complications between these 2 treatment strategies. In an earlier report on the PED, Siddiqui et al\textsuperscript{22} described a patient with a giant middle cerebral artery aneurysm treated with 2 PEDs and dense coil embolization. The patient had an acute thrombosis of the PED following the procedure, which was attributed to the dense coil mass. The authors recommended avoiding dense packing of aneurysms when coil embolization is used as an adjunctive treatment with the PED.

In a recent series published by Lin et al,\textsuperscript{23} 75 patients treated with the PED alone were compared with 29 patients treated with the PED and adjunctive coil embolization. There was no statistically significant difference in the complication rates between the 2 groups (10.3% with PED/coil versus 8.0% with PED alone, $P = .7$). Lin et al found, as we did in the IntrePED study, that aneurysms treated with a strategy of PED/coil were statistically larger than aneurysms treated with PED alone (16.3 versus 12.4 mm, $P = .02$). Nossek et al\textsuperscript{26} also found similar results in 25 consecutive patients with unruptured aneurysms treated with the PED and adjunctive coiling.

Szikora et al\textsuperscript{21} described their series of 19 patients with wide-neck intracranial aneurysms treated with a strategy of both PED/coil and PED alone. Initially, they treated patients with adjunctive coil embolization, maintaining low coil-packing densities; however, they switched to a strategy of overlapping PEDs without coiling in the latter part of their series. Despite the 2 differing strategies, they had similar occlusion rates at the 6-month follow-up interval. Although their overall complication rate (1 permanent nonrestricting morbidity and 1 mortality) was within the rates published in the literature, they did not specify which treatment strategy was associated with these complications.

In the IntrePED registry, there was a statistically significant difference in the aneurysm size between the 2 cohorts we evaluated ($P < .0001$). Aneurysms treated with adjunctive coil embolization were larger in both aneurysm size and aneurysm neck size. These differences are likely related to the individual clinician’s judgment in regard to the efficacy of stand-alone PED placement for this subset of aneurysms. There may have been a stronger desire to have more immediate contrast stasis during the initial treatment of larger aneurysms due to the higher chance of spontaneous rupture with increasing aneurysm size. In this instance, 2 options for increasing stasis would be to add coil embolization or to place multiple PEDs across the aneurysm neck. Potentially, the use of multiple PEDs may also increase the rate of complications during the procedure. However, we did not identify a difference in the percentage of aneurysms treated with multiple PEDs in either cohort. Patients with larger aneurysms, however, were more likely to have multiple PEDs deployed in both groups (PED alone versus PED/coil).

Another interesting finding in our analysis is the statistically significant difference in the location of aneurysms treated by either strategy. Again, this is likely related to clinical judgment in terms of the aneurysm characteristics and their relationship to the parent vessel. Additionally, endovascular surgeons may be more reluctant to use adjunctive coil embolization when using flow diverters in the posterior cerebral artery/posterior circulation, which is currently an off-label indication in some countries.

While one may presuppose a higher intraprocedural rupture rate with a strategy of PED and adjunctive coils, this was not apparent in our findings. Even with manipulation of the aneurysm wall/dome during coil embolization, there was no statistically significant increased rate of ipsilateral intracranial hemorrhage during or following the procedure. While the anatomical differences between the aneurysms in the 2 cohorts may have certainly influenced the practitioner’s judgment as to the optimal treatment strategy, there were no statistically significant differences in the primary or secondary end points for either treatment strategy. Overall, the complication rates reported for the patients in the IntrePED registry for either treatment strategy are in line with those in the published literature for use of flow-diverting stents.\textsuperscript{19}

Once the decision is made to use adjunctive coil embolization, the setup and performance of the procedure may be distinctly different from those used in deploying a PED alone. First, one must decide whether to coil the aneurysm before or after placement of the flow-diverting stent. One can choose to proceed first with primary or balloon-assisted coil embolization followed by PED deployment. While this strategy would not significantly affect the deployment of the PED from a guide catheter standpoint, it does add the time required to perform the initial embolization
to the overall procedure. Once coils are placed within the aneu-
rysm, the microcatheter or balloon microcatheter or both are re-
moved, allowing unencumbered navigation of the catheters for
PED deployment. This technique, however, can potentially ob-
scure visualization of the PED during deployment.

Alternatively, one can jail a microcatheter within the aneu-
rysm and initially place the PED followed by aneurysm coiling.
This strategy, however, may affect the choice of support catheters.
One must ensure that the inner diameter of the guide catheter is
sufficiently large enough to support simultaneous navigation of the
Marksman catheter (Covidien) and the microcatheter to be
used for coil embolization. The use of a second microcatheter
for coiling placed through the same guide catheter as the Marksman
catheter would likely preclude the use of additional catheters (ie,
distal-access catheters) to support PED deployment due to limi-
tations in guide-catheter size. Despite the increase in procedural
times and/or case complexity, there was no statistically significant
increase in the overall complication rate in terms of neurologic
morbidity and mortality in our analysis.

Limitations

Our study is limited by its retrospective nature, with participating
sites following their standard practice for treating aneurysms with
PEDs. As a result, the decision to use adjunctive coil embolization
was left to the discretion of the treating physician and was not
standardized across centers. Because the IntrePED study was a
retrospective, observational study without preplanned subgroup
analysis, no prespecified differences were expected between these
2 cohorts. Additionally, no power analysis was performed. While
there are certain inherent limitations with this type of study, we
believe that the conclusions may still be clinically relevant.

CONCLUSIONS

Decisions about which strategy to use when faced with a complex
cerebral aneurysm are made largely at the discretion of, and with
the judgment of, the practitioner. There have been few large series
comparing PED alone versus PED with coiling in terms of overall
efficacy in aneurysm treatment. While there was a statistically
significant difference in aneurysm size and location and proc-
dural times in the IntrePED registry between our 2 cohorts, there
was no statistically significant difference in overall complications.
These data suggest that either strategy represents an acceptable
risk profile in the treatment of complex cerebral aneurysms and
warrants further investigation.

ACKNOWLEDGMENTS

We thank Ms Suzanne LaScalza and Mei Jiang, PhD, for assistance
with statistical analysis. The IntrePED observational registry was
funded and supported by Covidien/Medtronic, with scientific
oversight of the study by the steering committee.

Disclosures: Min S. Park—RELATED: Other: Covidien/Medtronic. Comments: Covi-
dien provided statistical analysis support for the article (as described in our acknowl-
edgments). No money was provided as part of the preparation, writing, submission,
or any other aspects of this work. Philipp Taussky—RELATED: Consulting Fee or
Honorarium: Covidien/Medtronic (Pipeline proctor). David F. Kallmes—RELATED:
Grant: ev3/Covidien/Medtronic.* Comments: support for clinical trial. Consulting
Fee or Honorarium: ev3/Covidien/Medtronic.* Comments: Steering Committee for
clinical trial; Fees for Participation in Review Activities, Such as Data Monitoring
Boards, Statistical Analysis, Endpoint Committees, and the Like: ev3/Covidien/
Medtronic.* Comments: Safety Committee; UNRELATED: Board Membership: GE
Healthcare Cost-Effectiveness Board;* Consultancy: ev3/Covidien/Medtronic.*
Comments: clinical trials: support: Grants/Grants Pending: MicroVention,* Codman
Neuro/DePuy Synthes,* NeuroSigma,* SurModics,* Sequent Medical,* ev3/Covi-
dien/Medtronic,* Comments: support for clinical and preclinical research; Patents
(licensed/pending or issued);* Mayo Medical Ventures,* Comments: augmenting patent;
Royalties; University of Virginia Patent Foundation [Spine Fusion]; Travel/
Accommodations/Meeting Expenses Unrelated to Activities Listed: ev3/Covi-
dien/Medtronic.* Comments: travel to FDA panel meeting: Elad I. Levy—UNRELATED:
Board Membership: Stryker [American Spinal Injury Association Impairment Scale
[AIS] Clinical Advisory Board]; Next-Gen Biologies [Advisory Board]. Consultancy:
Pulsar Vascular (unpaid); Expert Testimony: renders medical/legal opinion as an ex-
pert witness; Payment for Lectures (including service on Speakers Bureaus): Covidi-
en/Medtronic [honorarium for lectures]; Stryker: Payment for Development of
Educational Presentations: Covidien/Medtronic Abbott; Comments: honorarium for
training for Covidien/Medtronic and carotid training sessions for Abbott for
physicians; Stock/Stock Options: Blockade Medical, Intratech Medical, Medtronic
Medical, Other: Covidien/Medtronic [National Principal Investigator for Solitaire with
the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Isch-
emic Stroke trials]. Pascal Jabbour—UNRELATED: Consultancy: Covidien (Pipeline
proctor). István Szikora—RELATED: Consulting Fee or Honorarium: Covidien/
Medtronic; Support for Travel to Meetings for the Study or Other Purposes: Covi-
dien/Medtronic; UNRELATED: Consultancy: Covidien/Medtronic, Stryker, Codman,
Sequent Medical. Edoardo Boccardi—RELATED: Consulting Fee or Honorarium: Co-
vien/Medtronic/Medtronic; UNRELATED: Consultancy: Covidien/Medtronic, Stryker,
Mi-
croVention. Ricardo A. Hanel—RELATED: Consulting Fee or Honorarium: Covidien/
Medtronic; UNRELATED: Board Membership: Medtronic Medical; Consultancy: Stryker,
Codman, MicroVention; Stock/Stock Options: Blockade Medical. Alain Bonafé—
UNRELATED: Consultancy: Covidien/Medtronic. Cameron G. McDougall—RELATED:
Consulting Fee or Honorarium: Covidien/Medtronic; UNRELATED: Consultancy: MicroVention.* Money paid to the institution.

REFERENCES

1. Fiorella D, Woo HH, Albuquerque FC, et al. Definitive reconstruc-
tion of circumferential, fusiform intracranial aneurysms with the
Pipeline embolization device. Neurosurgery 2008;62:1115–20; dis-
cussion 1120–21 CrossRef Medline
struction of cerebral aneurysms with the Pipeline embolization
discussion 642–43; quiz N6 CrossRef Medline
for the intracranial treatment of aneurysms trial. AJNR Am J Neu-
orad 2011;32:34–40 CrossRef Medline
Pipeline embolization device in 100 small intracranial aneurysms.
5. Zanaty M, Chalouhi N, Starke RM, et al. Flow diversion versus con-
tentional treatment for carotid cavernous aneurysms. Stroke 2014;
45:2656–61 CrossRef Medline
6. Tse MM, Yan B, Dowling RJ, et al. Current status of Pipeline embo-
lization device in the treatment of intracranial aneurysms: a review.
World Neurosurg 2013;80:829–35 CrossRef Medline
using the Pipeline flow-diverting embolization device: a single-cen-
ter experience with long-term follow-up results. AJNR Am J Neuro-
orad 2012;33:1436–46 CrossRef Medline
device (PED) for neurovascular reconstruction: initial experience
in the treatment of 101 intracranial aneurysms and dissections.
Neuroradiology 2012;54:369–82 CrossRef Medline
results following treatment of unruptured intracranial aneurysms
with the Pipeline embolization device. AJNR Am J Neurorad 2012;
33:164–70 CrossRef Medline
with Pipeline stent: feasibility, technique, and complications. Neu-
orad 2012;71:679–91; discussion 691 CrossRef Medline


