Pipeline Embolization Device for Treatment of Intracranial Aneurysms—The More, the Better? A Single-center Retrospective Observational Study

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Abstract

Objectives—The pipeline embolization device (PED) is a treatment option for wide-neck intracranial aneurysms. The individual number of implants needed to securely exclude an aneurysm is unknown. Our primary objective was to compare midterm occlusion and complication rates in aneurysms treated with a single versus multiple PEDs without adjunctive coiling in a single procedure.

Patients and methods—Fifty-five patients harboring 58 intracranial aneurysms were treated with 121 PEDs between March 2011 and December 2013. About 38 aneurysms in 37 patients were treated exclusively with PED without adjunctive coiling in a single procedure. All pretreated (recurrent) aneurysms were excluded from analysis. Occlusion results were rated using the OKM-scale. Periprocedural complications were recorded.

Results—Immediate angiographic results showed favorable obliteration (OKM C1-3+D) in 5/20 (25%) single-PED cases versus 8/18 (44%) in multiple-PED cases (p=0.3); complete obliteration (OKM D) was achieved in 4/20 (20%) with single-PED versus 5/18 (28%) in the multiple-PED group (p=0.2). Midterm (median: 7 months) angiographic rates of favorable occlusion were significantly higher in the multiple-PED group: 14/20 (70%) in single-PED cases versus 15/15 (100%) in multiple-PED cases (p=0.03); complete occlusions were observed in 12/20 (60%) single-PED cases versus 14/15 (93%) in multiple-PED cases (p=0.05). Retreatment was necessary in 3/20 single-PED (15%) and in none of the multiple-PED cases. Procedural complications did not differ between groups.

Conclusion—The nonstaged use of multiple PEDs may result in a higher rate of favorable occlusions at midterm in wide-neck aneurysms treated without adjunctive coiling without significantly increasing the rate of procedural complications.

Keywords

aneurysm; endovascular; flow diversion; pipeline

PED pipeline embolization device
OKM O’Kelly-Marotta scale
ASA acetylsalicylic acid
CPG clopidogrel
DSA digital subtraction angiography
FU follow-up
HH Hunt & Hess classification
ICA internal carotid artery

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MCA  middle cerebral artery

mRS  modified Rankin Scale

INTRODUCTION

The pipeline embolization device (Covidien, Irvine, California, USA) is a flexible self-expanding flow diverting stent. It is designed to achieve aneurysm occlusion by means of endoluminal reconstruction of the segment that gives rise to the aneurysm. The PED received CE mark in July 2009. The device has proven to be efficient in maintaining stable aneurysm occlusion in wide-neck intracranial aneurysms; its safety profile has been shown to be favorable in several studies [1–3]. However, the number of PEDs needed to permanently and securely occlude an individual aneurysm depends on rheological and hemostasiological factors; therefore, it is not predefined and remains subject of debate at present [4]. In addition, a major concern with flow diverters is their frequent inability to immediately occlude the aneurysm with the risk of aneurysm rupture during the “latency” period [5]. The primary aim of this study was to compare midterm aneurysm occlusion rates in view of the procedural complication rates in patients treated with a single versus multiple PEDs without adjunctive coiling in a single endovascular procedure, excluding staged treatments.

Materials and methods

Patient population

Between March 2011 and December 2013, 55 patients harboring 58 intracranial wide-neck aneurysms were treated with a total of 121 PEDs. Thereof, 38 aneurysms in 37 patients were treated with PED alone without adjunctive coiling in a single procedure. All pretreated aneurysms and staged multiple PED implantations were excluded from this analysis. The patient population was divided into two groups based on single-layer PED versus multiple-layer (≥2) PED application during the aneurysm treatment.

Nineteen patients (51%) harboring 20 aneurysms (53%) were treated with a single PED, while 18 patients (49%) with 18 aneurysms (47%) were treated with two or more PEDs. A comparison between both groups was made for the postinterventional angiographic result, midterm aneurysm obliteration, the need for retreatment, periprocedural complications and delayed adverse events and clinical outcome. Angiographic aneurysm occlusion was categorized with the use of the OKM-grading-scale [6] for the assessment of intracranial aneurysms treated with flow-diverting stents. The OKM scale utilizes both the amount of contrast filling (filling grades A;B;C;D) and the persistence of contrast in the aneurysmal lumen with regard to the angiographic phase (stasis grades 1,2,3) (Table 1).

Follow-up was performed by routine control DSA executed after a median of 222 days in the single-PED group and after a median of 196 days in the multiple-PED cohort. The clinical outcome (mRS) was established by a consultant neurosurgeon at the time of the follow-up angiography.

Treatment technique

All elective patients received double antiplatelet medication (75 mg/d CPG, 100 mg/d ASA) started 5 days before the procedure and maintained for 3 months after the treatment, followed by permanent single antiplatelet treatment with either CPG or ASA. Platelet inhibition was tested in all patients with ASA and P2Y12 assays (VerifyNow, Accumetrics, San Diego, California). A platelet inhibition level between 30–90% for CPG and 350-550 ARU (aspirin response units) for ASA was required. Insufficient response to either drug was counteracted by dose escalation (e.g., CPG 150 mg/d) or substitution with prasugrel (40 mg bolus, 5 mg/day). A bolus of heparin (5000 IU) was administered after groin puncture, followed by aliquots of 1000 IU/h. Heparin was discontinued at the end of the procedure.

In acute cases with SAH, tirofiban was applied intravenously peri-interventionally followed by ASA and CPG 16–24h later.

All PEDs were deployed by the same operator through a dedicated microcatheter (Marksman, Covidien). Inadequate vessel wall apposition had to be counteracted by means of balloon angioplasty in 5% of the single and 33% of the multiple-PED cases. The number of PEDs deployed was based on visual assessment of the angiographic result applying the OKM scale of intra-aneurysmal stasis. In all cases without a visible change in stasis, indicating an insufficient immediate effect, the application of an additional PED was conducted.

Table 1. OKM scale for the assessment of intracranial aneurysms treated with flow-diverting stents.

<table>
<thead>
<tr>
<th>Stasis grade ▲</th>
<th>Arterial</th>
<th>Capillary</th>
<th>Venous</th>
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<tbody>
<tr>
<td>A (&gt;95%)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>B (5-95%)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>C (&lt;5%)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D (0%)</td>
<td>Angiographic phases irrelevant with no filling</td>
<td></td>
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The application of the PED in both groups was performed as previously described, aiming at a maximal mesh density across the aneurysm neck by both avoiding oversizing of the implant, applying a push–pull technique and in all cases of multiple PEDs by insuring complete multilayer coverage of the aneurysm orifice [7].

All included aneurysms were treated in a single procedure, comprising a “case.” Therefore, the terms are used synonymously for descriptive purposes.

**Data Analysis**

Continuous study parameters were compared between patients by either Welch t-test in case of a normal distribution or by the Mann–Whitney U-test in case of non-normal or ordinal distribution. Fisher’s exact test was used for categorical variables. All statistical analyses were performed using Graph Pad Prism V.6.1 (Graphpad Software, La Jolla, California, USA), the significance level was set at α=0.05.

**RESULTS**

A single PED was used in 20 (53%), two PEDs in 9 (23%) and three PEDs in 8 (21%) aneurysms; one aneurysm (3%) was treated with four PEDs. Of 27/38 (71%) cases were elective procedures, 11 (29%) cases were performed in acute SAH cases without any difference in distribution between the multiple-PED group (5/18 cases, 28%) and the single-PED group (6/20, 30%). The proportion of female patients did not differ between groups, comprising 85% (17/20) in the single-PED group and 78% (14/18) in the multiple-PED group. There was no difference in the mean age (53.6 years (SD ± 12.0) in the single-PED, 55.8 years (SD ± 12.7) in the multiple-PED group). The aneurysms in the multiple-PED group were larger (mean sac diameter of 8.3 mm (SD ± 4.1) versus 4.9 mm (SD ± 3.8), p=0.01) and had a more unfavorable neck width (6.9 mm (SD ± 2.8) vs. 4.8 mm (SD ± 2.3), p=0.03). More aneurysms ≥10 mm were treated with multiple PEDs (8/18, 44% vs. 3/20, 15%; no statistical significance). 90% of single PED and 67% of multiple PED-treatments were performed in the anterior circulation. There was no difference in the distribution of fusiform, blister or dissecting aneurysms between the groups; they accounted for 20% (4/20) in the single-PED group versus 33% (6/18) in the multi-PED group (p>0.05). Balloon remodeling of the PED was performed in 6/18 (33%) in the multiple-PED group and in 1/20 (5%) in the single-PED group.

**Angiographic Results**

There was no significant difference in favorable (OKM C1-3+D) or complete angiographic occlusion (OKM D) immediately after PED implantation between groups: Favorable obliteration (C1-3+D) was seen in 5/20 cases (25%) in the single- group versus 8/18 (44%) in the multiple-PED group (p=0.3), complete obliteration (D) was achieved in 4/20 (20%) in the single vs. 5/18 (28%) in the multiple group (p=0.2).

Angiographic follow-up was available for all cases in the single-PED group and for 15/18 cases (83%) of the multiple-PED group. The median follow-up interval was slightly longer in the single-PED (222 days; range 161–865 days) compared to the multiple-PED group (196 days, range 137–930 days). At midterm follow-up, the rate of favorable and complete occlusion differed significantly between the groups: complete occlusion was reached in 14/15 cases (93%) in the multiple-PED group versus 12/20 (60%) cases in the single-PED group (p=0.05). A favorable angiographic outcome was also significantly more frequent in the multiple-PED group 15/15 (100%) versus 14/20 (70%) in the single-PED group (p=0.03, Table 2). Retreatment of the target aneurysm was necessary in 3/20 cases in the single-PED cases (15%); there were no retreatments in the multiple-PED group. Retreatment was performed in one case of a ruptured blister aneurysm that regrew within days. In another case, it was necessary because of unchanged angiographic filling and stasis grade (B1) at first and second follow-up DSA performed one year after treatment. Worsening of the stasis grade within days (A3→A2) was the reason for retreatment in another case. All cases were treated by implantation of additional PED.

### Table 2. Angiographic outcome by treatment group.

<table>
<thead>
<tr>
<th></th>
<th>Single-PED</th>
<th>Multiple-PED</th>
<th>p value</th>
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<tbody>
<tr>
<td>Neck width, mm (mean ± SD)</td>
<td>4.8 (± 2.3)</td>
<td>6.9 (± 2.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Max. aneurysm sac diameter, mm (mean ± SD)</td>
<td>4.9 (± 3.8)</td>
<td>8.3 (± 4.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Initial result “complete occlusion”(OKM C1-3 + D)</td>
<td>5/20 (25%)</td>
<td>8/18 (44%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Initial result “favorable occlusion”(OKM D)</td>
<td>4/20 (20%)</td>
<td>5/18 (28%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FU result “favorable occlusion”(OKM C1-3 + D)</td>
<td>14/20 (70%)</td>
<td>15/15 (100%)</td>
<td>0.03</td>
</tr>
<tr>
<td>FU result “complete occlusion” (OKM D)</td>
<td>12/20 (60%)</td>
<td>14/15 (93%)</td>
<td>0.05</td>
</tr>
<tr>
<td>FU interval, median days (range)</td>
<td>222 (161–865)</td>
<td>196 (137-930)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. not statistically significant.
Complications and adverse events
The frequency of periprocedural complications did not differ between groups: There was one in-stent thrombosis in each group (5.5% of the multi-PED and 5% of the single-PED). In addition, we recorded two device-related events: a pusher wire breakage and a loss of the PED capture coil. These could not be specifically attributed to the use of multiple PEDs. However, one of these events occurring in the multiple-PED group potentially resulted in a worsening of the neurological status. This patient was referred with a severe SAH from a dissecting P2/3 aneurysm. An attempt to reconstruct the artery with multiple PEDs had failed after detachment of the capture coil in P3. Trying to retrieve it resulted in a vessel perforation and the artery had to be occluded with coils. The clinical outcome was poor but most likely due to severe vasospasm induced by the initial SAH and resulting in multiple territorial infarctions that were most pronounced in other vascular territories, such as the MCA and the contralateral PCA-territory. There were no late adverse events during FU.

Clinical follow-up
Clinical FU was available for all 38 cases. All elective patients (27/38, 71%) showed an excellent outcome (mRS 0). In acute SAH cases, a favorable outcome (mRS 0–2) was seen in 2/5 (40%) cases in the multiple-PED group and in 5/6 (83%) cases in the single-PED group. All cases with an unfavorable clinical outcome were severely affected due to their SAH at the time of the treatment: Two patients in the multi-PED group were HH4, one was HH5. The patient in the single-PED group was HH4.

DISCUSSION
Since its first approval under the CE mark in 2009, the PED has been increasingly used for the treatment of intracranial aneurysms in various anatomic locations with adequate safety and efficacy [8–12]. With regard to flow diversion as a general concept in aneurysm treatment, however, there is an on-going debate on the amount of surface coverage across the aneurysm neck that is needed to safely and permanently exclude it from the circulation. Furthermore, it is a major concern that flow diverters are frequently incapable to achieve an immediate aneurysm occlusion with the risk of aneurysm rupture during the latency period [5]. Apart from choosing the appropriate size of the implant with specific avoidance of oversizing that would result in decreased metal coverage of the neck and application of the PED under controlled forward pressure [7], the issue of surface coverage can be addressed by either increasing the mesh density of the individual implant or by using multiple implants. In our series, there were in fact numerical differences in favorable and complete occlusion rates between the two groups initially, directly after the deployment of the PEDs. These failed to reach statistical significance mainly because of sample size (25% vs. 44% in favor of multiple PEDs, Table 2). Since we did not know the amount of coverage that would be needed to securely exclude an individual aneurysm a priori, there was no predefined “stopping-point.” If for example an aneurysm that was deemed to be at a high risk of rupture showed no angiographic effect after one PED (OKM A1), decision was made to place an additional PED. In trying to balance aneurysm occlusion with a potential risk of unwanted side branch coverage, we eventually stopped after the second PED placement even though the immediate result was improved but would still not qualify as “favorable occlusion” (i.e., OKM A3= still filling but stasis inside the sac).

It would be a natural assumption that the efficacy of flow diversion increases with the number of layers of any given type of stent. In patient treatment, this would prompt the decision to use multiple PEDs in those cases where the remaining inflow after a single implant is deemed to indicate inadequate long-term results. Contrary to this assumption, Chalouhi et al. have published a comparison of two groups within their own series in which they did not find a significant difference between single- and multiple-PED treatments with regard to initial and long-term occlusion rates [13]. They did further report a higher incidence of complications with multiple PEDs (15% vs. 5%). In their series, this might be explained by the fact that despite reaching statistical significance for each parameter, a higher portion of patients in their multiple-PED group might be considered as “high-risk.” In their series, patients in the multiple-PED group were significantly older, the mean aneurysm size was larger, and the proportion of aneurysms arising from the posterior circulation was larger including those arising from the basilar trunk. Also, the proportion of fusiform and dissecting aneurysms was almost twice as high in their multiple-PEDs group. In contrast to our series which excluded pretreated aneurysms as well as adjunctive coiling, the latter was performed in 11% of aneurysms treated with a single PED versus 6% of those treated with multiple PEDs in Chalouhi’s report, which might have compensated for otherwise inefficient intra-aneurysmal flow reduction in the single PED group.

In our series, the mean aneurysm size and the mean neck width were significantly higher in the multiple-PED
more large aneurysms (≥10 mm) were treated with multiple PED. Although these aneurysms are known for inferior midterm occlusion rates compared to smaller aneurysms with favorable neck width, the use of multiple PED in a single procedure (exclusively non-staged treatments) yielded very satisfactory midterm results without a difference in the incidence of procedural complications and late adverse events between the groups. There was one in-stent thrombosis in each group; the other two were true mechanical failures in the multi-PED group that did occur during placement of the first implant. Therefore, we do not share the impression of Chalouhi et al., that the procedural technical difficulty increases with the number of PEDs used with the exception of good visibility being hampered by previously placed PEDs. In particular, there were no delayed complications such as distal parenchymal hemorrhage or spontaneous delayed rupture, which have been reported in the literature [14–16].

Our observations confirm the assumption that more struts are more efficient in the midterm follow-up results. The hemodynamic effect was more pronounced with multiple PEDs for both OKM C1-3 and D but failed to reach statistical significance in the early phase; it did though reach statistical significance in the midterm follow-up angiographies. Furthermore, retreatment was only necessary in the single-PED group (3 cases, 15%) but not in the multiple-PED group. One ruptured blister-type paraophthalmic aneurysm had increased in size after initial single PED placement and needed to be retreated with two additional PEDs (Figure 2 A–D); this patient was only counted in the single-PED group according to the intention to treat approach. Balloon angioplasty was more frequently performed in the multiple-PED group, mainly in order to achieve satisfactory wall adaptation of the additional device. This might be a drawback of the technique; it should be controlled for in larger cohorts.

Figure 1. A–C: Large paracavernosal LICA aneurysm presenting with ophthalmoplegia. Angiograms before (A), immediately after placement of three overlapping PEDs (B) and FU at six months (C). At six months, the clinical symptoms had completely disappeared.

Figure 2. A–D: Paraophthalmic blister type aneurysm. Before endovascular treatment (A), immediately after placement of one PED (B), and FU at 16 days (C): The aneurysm recurred early, increased in size and transformed into a saccular type. Retreatment was successfully performed with two additional PEDs; at six months, the entire segment including the aneurysm had remodeled (D).
Chalouhi et al. identified the use of multiple PEDs as an independent predictor of complications and poor outcome. Based on our experience and the fact that both groups conducted a pure retrospective analysis, we postulate that patient-related and anatomical factors listed above (which failed to reach significance) most likely prompted the use of multiple PEDs, thus leading to an overrepresentation of technically “demanding” cases, which most likely explains the differences in safety. The fact that Chalouhi et al. did not find a significant difference in the proportion of >90%-occlusion rates independent of any safety issues might be attributed to sample size or patient selection and is at least counterintuitive to the very concept of flow diversion, that—if taken to the extreme of 100% metal coverage—would invariably lead to aneurysm exclusion.

**Limitations of our study**

These are mainly caused by a small sample size and the heterogeneity of any such population as presented here. The anatomic location, anterior or posterior circulation, does probably play a lesser role in that respect than do patient specific differences in tortuosity, blood pressure (and therefore flow velocity), blood viscosity, platelet function, etc. Other problems are the lack of a study protocol and the limitations of immediate per-treatment quantification of the flow diversion effect, that is, “when to stop.” Arguably, it might not play a role if occlusion occurs later with a single PED as long as it does occur eventually. The problem in an individual patient is, that the operator has no other measure to predict long term outcome, than the visual interpretation of the per treatment angiogram. Finally, despite equal median follow-up periods, for some individuals, they vary significantly.

To answer the question of how much metal coverage is sufficient yet safe in most of the cases treated with a specific flow diverting implant, a larger group, allowing for a matched pair analysis, would be needed. Based on our experience, we believe that despite good results with single PED in large series, a certain subset of patients does require the use of overlapping multiple PEDs to insure sufficient flow diversion and ultimately aneurysm occlusion.

**CONCLUSION**

In our series, the use of multiple PED in a single procedure did not lead to an increase in procedural complications and late adverse events. Multiple PEDs resulted significantly more often in an angiographically favorable occlusion result at midterm follow-up despite their application in aneurysms with more unfavorable attributes.

**Contributorship Statement**

Christoph Kabbasch performed manuscript writing, data sampling, patient treatment; Anastasios Mpotsaris carried out data sampling, manuscript editing; Daniel Behme performed statistics, manuscript editing; Franziska Dorn manuscript editing, patient treatment; Panteidis Stavrinou performed clinical status and FU examinations, manuscript editing; Thomas Liebig concept and manuscript writing, patient treatment

**Competing Interests Statement**

The authors declare that they have the following potential competing interest: Christoph Kabbasch, Daniel Behme, Franziska Dorn, Daniel Behme, and Pantelis Stavrinou disclose nothing. Anastasios Mpotsaris consults for Penumbra Inc., Sequent Medical, and Neuravi. Thomas Liebig previously consulted for Covidien (terminated 2014), consults and proctors for Sequent Medical.

**Ethics approval statement**

According to the guidelines of the local ethics committee, no approval was necessary.

**Data-sharing statement**

All data will be made available upon request in an anonymized manner.

**Funding statement**

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**REFERENCES**


