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ABSTRACT

BACKGROUND AND PURPOSE: Tandem aneurysms are defined as multiple aneurysms located in close proximity on the same parent vessel. Endovascular treatment of these aneurysms has rarely been reported. Our aim was to evaluate the safety and efficacy of a single Pipeline Embolization Device for the treatment of tandem aneurysms of the internal carotid artery.

MATERIALS AND METHODS: A retrospective analysis of consecutive aneurysms treated with the Pipeline Embolization Device between 2009 and 2016 at 3 institutions in the United States was performed. Cases included aneurysms of the ICA treated with a single Pipeline Embolization Device, and they were divided into tandem versus solitary. Angiographic and clinical outcomes were compared.

RESULTS: The solitary group (median age, 58 years) underwent 184 Pipeline Embolization Device procedures for 184 aneurysms. The tandem group (median age, 50.5 years) underwent 34 procedures for 78 aneurysms. Aneurysms were primarily located along the paraophthalmic segment of the ICA in both the single and tandem groups (72.3% versus 78.2%, respectively, $P = .53$). The median maximal diameters in the solitary and tandem groups were 6.2 and 6.7 mm, respectively. Complete occlusion on the last angiographic follow-up was achieved in 75.1% of aneurysms in the single compared with 88.6% in the tandem group ($P = .06$). Symptomatic thromboembolic complications were encountered in 2.7% and 8.8% of procedures in the single and tandem groups, respectively ($P = .08$).

CONCLUSIONS: Tandem aneurysms of the ICA can be treated with a single Pipeline Embolization Device with high rates of complete occlusion. While there appeared to be a trend toward higher thromboembolic complication rates, this did not reach statistical significance.

ABBREVIATION: PED = Pipeline Embolization Device

Multiple intracranial aneurysms account for 14%–34% of the distribution of all intracranial aneurysms.^{1–5} When these aneurysms are located in close proximity to each another on the same parent vessel, they are referred to as “tandem aneurysms.” The treatment of tandem aneurysms has rarely been reported in the literature. These aneurysms are most commonly found along the internal carotid artery and may arise within the same anatomic segment or involve adjacent segments. Rarely, they are identified in the posterior circulation.^{1,6–9} Flow diversion with the Pipeline Embolization Device (PED; Covidien, Irvine, California) was initially approved by the US Food and Drug Administration

for treatment of large or giant, wide-neck cerebral aneurysms of the ICA from the petrous to superior hypophyseal segments.¹⁰ Numerous studies have since demonstrated the safety and efficacy of the PED in the treatment of aneurysms with varying morphologies and anatomic locations.^{11–16} Currently, only a few studies with small numbers of patients have evaluated endovascular treatment of tandem aneurysms with coil embolization,⁸ stent-assisted coiling,⁹ or flow diversion.⁹ In this study, we compare the outcomes following deployment of a single PED in 2 groups of patients, those with solitary ICA aneurysms and those with tandem ICA aneurysms.

MATERIALS AND METHODS

A retrospective analysis of consecutive aneurysms treated with PED deployment between 2009 and 2016 at 3 academic institutions in United States was performed. Inclusion criteria consisted of all adult patients with saccular intracranial ICA aneurysms treated with a single PED. Both ruptured and unruptured aneurysms were included. Patients were then divided into 2 groups: solitary aneurysms and tandem aneurysms. Tandem aneurysms

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consisted of >1 intracranial ICA aneurysm within the same anatomic segment or involving adjacent anatomic segments. We collected the following information: patient demographics, aneurysm and PED characteristics, procedural complications, and angiographic and functional outcomes. Institutional review board approval was obtained at all 3 centers before commencement of the study.

Procedural Details

Patients undergoing elective aneurysm treatment received aspirin, 325 mg, and clopidogrel, 75 mg, daily for 3–14 days before the intervention. Platelet function testing was routinely performed with whole-blood lumi-aggregometry, light transmission aggregometry, or the VerifyNow P2Y12 assay (Accumetrics, San Diego, California). Clopidogrel nonresponders were identified on the basis of established cutoff values at the individual institutions and were guided by manufacturer's recommendations. If a patient was identified as a clopidogrel responder, clopidogrel was continued. If a patient was identified as a clopidogrel nonresponder, the choice to continue the same dose of clopidogrel, administer a 1-time 600-mg clopidogrel boost within 24 hours of the procedure, or switch to ticagrelor was at the discretion of the interventionalist performing the procedure. Patients undergoing treatment of a ruptured aneurysm received a loading dose of aspirin, 650 mg, and clopidogrel, 600 mg, immediately before the intervention. Patients underwent local anesthesia with sedation or general anesthesia at the discretion of the individual institutions, and all patients were anticoagulated with heparin throughout the procedure, with an activated clotting time target of 250–300 seconds. The type of the guide catheter and microcatheter used for PED deployment was at the discretion of the individual institutions. The deployment and apposition of the PED to the ICA wall was documented by fluoroscopy. Dual antiplatelet therapy was continued for at least 3 months after the procedure, and aspirin, indefinitely thereafter.

Angiographic and Clinical Outcome

Angiographic outcome was assessed with digital subtraction angiography or MR angiography based on follow-up protocols used at each individual institution. Aneurysm occlusion on follow-up DSA imaging was assessed by the treating interventionalist. Follow-up MRAs were assessed by a diagnostic radiologist and the treating interventionalist. Occlusion was categorized as complete occlusion (100%), near-complete occlusion (90%–100%), and partial occlusion (< 90%). Functional outcomes were assessed by using the modified Rankin Scale at last follow-up.

Statistical Analysis

Statistical analysis was performed by using SPSS, Version V 21.0 (IBM, Armonk, New York). In univariate analysis, variables were compared between groups with the Mann-Whitney *U* test for nonparametric numeric variables and the χ^2 test for categorical variables. Statistical significance was defined as $P < .05$. Multivariate logistic regression was performed on candidate predictor variables to identify independent differences in outcome between both groups.

RESULTS

Baseline Characteristics

The solitary aneurysm group (median age, 58 years) underwent 184 PED placement procedures for the treatment of 184 aneurysms, and the tandem aneurysm group (median age, 50.5 years) underwent 34 PED placement procedures for the treatment of 78 aneurysms. Current smoking was identified in 22.8% and 52.9% of patients undergoing procedures in the solitary and tandem groups, respectively ($P < .001$). The pretreatment mRS was 0–2 in 97.8% and 94.1% of procedures in the solitary and tandem aneurysm groups, respectively ($P = .23$). Treatment of acute aneurysmal subarachnoid hemorrhage occurred in 2.2% and 8.8% of procedures in the solitary and tandem aneurysm groups, respectively ($P = .11$).

Aneurysm Characteristics

Aneurysms were primarily located along the paraophthalmic segment of the ICA in both the solitary and tandem aneurysm groups (72.3% versus 78.2%, respectively, $P = .53$). The median maximal diameter of the aneurysm was 6.2 mm in the solitary aneurysm group and 6.7 mm in the tandem aneurysm group. The median neck diameter of the aneurysm was 4 mm in the solitary group and 3.9 mm in the tandem group (Table 1). Aneurysms other than the largest aneurysm in the tandem aneurysm group had a median maximal diameter of 3 mm (range, 1–12 mm) and a median neck width of 2.4 mm (range, 1–6 mm). This finding was significantly different from the respective measurements of the largest treated aneurysm in the tandem aneurysm group and the solitary aneurysm group ($P < .001$ and $P < .001$, respectively) (Table 2). A daughter sac was present in 25.1% and 15.4% of aneurysms in the single and tandem aneurysm groups, respectively ($P = .08$).

Treatment Outcome

There was no significant difference in the length of the procedure in the treatment of solitary aneurysms compared with tandem aneurysms (69.5 versus 76 minutes, respectively, $P = .52$). Similarly, there was no significant difference in the length ($P = .42$) or diameter ($P = .26$) of PEDs used in either group. The median length of angiographic follow-up was significantly longer in the tandem aneurysm group compared with the solitary aneurysm group, 18 months (mean, 19.2 months) versus 12 months (mean, 15.4 months), respectively ($P = .008$). On the last angiographic follow-up, complete occlusion was achieved in 75.1% of aneurysms in the solitary aneurysm group compared with 88.6% in the tandem aneurysm group ($P = .06$). After stratifying the tandem aneurysm group into the largest aneurysm and other aneurysms within the tandem group, the rate of complete occlusion was not significantly higher compared with solitary aneurysms ($P = .21$) (Table 3). Retreatment was performed in 4.9% and 5.7% of the solitary and tandem aneurysm groups, respectively ($P = .81$). At last follow-up, the mRS improved in 27.5% and 27.3% of patients and worsened in 7% and 0% of the solitary and tandem aneurysm groups, respectively ($P = .33$). Symptomatic thromboembolic complications were encountered in 2.7% and 8.8% of procedures in the solitary and tandem aneurysm groups, respectively ($P = .08$). Symptoms were permanent (lasting >30 days) in 1.6% and 2.9% of procedures, respectively ($P = .60$). One procedure for the

Table 1: Baseline characteristics

Parameter	Solitary Aneurysm	Tandem Aneurysms	P Value
No. of PEDs placed	184	34	—
Aneurysms treated with single PED	184	78	—
1	184	—	—
2	—	28	—
3	—	3	—
4	—	2	—
5	—	1	—
Sex			
Female	166 (90.2%)	31 (91.2%)	.86
Male	18 (9.8%)	3 (8.8%)	
Median age (median) (range) (yr)	58 (24–82)	50.5 (19–75)	.006
Smoking (No.)	42 (22.8%)	18 (52.9%)	<.001
Pretreatment mRS (No.)			
0–2	180 (97.8%)	32 (94.1%)	.23
3–5	4 (2.2%)	2 (5.9%)	
Aneurysm location			
Cavernous	25 (13.6%)	7 (9%)	.53
Paraophthalmic	133 (72.3%)	61 (78.2%)	
Posterior communicating	26 (14.1%)	10 (12.8%)	
Aneurysm measurements (median) (range) (mm)			
Maximal diameter	6.2 (1.6–28.3) ^a	6.7 (2–40)	.48
Neck size	4 (1–14.3) ^b	3.9 (1.8–8.5) ^c	.14
Daughter sac (No.)	46 (25.1%)	12 (15.4%)	.08
Subarachnoid hemorrhage (No.)			
Acute (<2 weeks)	4 (2.2%)	3 (8.8%)	.11
Remote (>2 weeks)	19 (10.3%)	2 (5.9%)	
Prior treatment (No.)			
Endovascular	23 (12.5%)	2 (2.6%)	.031
Surgery	6 (3.3%)	0	
Both	2 (1.1%)	1 (1.3%)	
Clopidogrel responders (No.)			
Yes	123 (68.7%) ^d	24 (75%) ^e	.48
No	56 (31.3%)	8 (25%)	

^a Data are missing for 25 aneurysms.^b Data are missing for 50 aneurysms.^c Data are missing for 2 aneurysms.^d Data are missing for 5 procedures.^e Data are missing for 2 procedures.**Table 2: Aneurysm size**

Parameter	Solitary Aneurysm	Tandem Aneurysms	
		Largest Aneurysm	Other Aneurysms
Median maximal diameter (range) (mm)	6.2 (1.6–28.3) ^{a,b}	6.7 (2–40) ^b	3 (1–12) ^b

^a Data are missing for 25 aneurysms.^b $P < .001$.**Table 3: Occlusion rate**

Occlusion Rate	Solitary Aneurysm	Tandem Aneurysms		P Value
		Largest Aneurysm	Other Aneurysms	
Complete (100%)	109 (75.1%) ^a	36 (90%) ^b	26 (86.6%) ^b	.21
Near-complete (90%–99%)	12 (8.3%)	2 (5%)	2 (6.7%)	
Partial (<90%)	24 (16.6%)	2 (5%)	2 (6.7%)	

^a Data are missing for 39 aneurysms.^b Data are missing for 4 aneurysms.

treatment of a solitary aneurysm was complicated by both an ischemic stroke and an intraparenchymal hemorrhage. There were no mortalities in either group (Table 4).

DISCUSSION

In this study, we report a multicenter experience with single PED placement for the treatment of tandem intracranial aneurysms of the internal carotid artery. Factors that influenced the decision to attempt treatment of tandem aneurysms with a single flow diverter included close proximity of the aneurysms, a favorable local angioarchitecture of the parent vessel, and small aneurysm size. Tandem aneurysms were compared with solitary aneurysms with respect to rates of aneurysm occlusion and complications. Complete occlusion rates were higher in the tandem aneurysms group compared with solitary aneurysms, with a trend toward statistical significance. A potential confounder was the small size of the adjacent aneurysms in the tandem group when the largest aneurysm was excluded. Therefore, after stratifying tandem aneurysms based on size, the difference was not statistically significant (Table 3). Despite a trend toward higher symptomatic thromboembolic complication rates in the tandem group, no statistically significant difference was identified. These findings mirror a prior study that associated a higher aneurysm occlusion rate but also procedural complications with simultaneous treatment of multiple aneurysms with the PED.¹³

Endovascular Treatment of Tandem Aneurysms

The surgical management of tandem aneurysms can be challenging, especially when paraophthalmic or posterior circulation sites are involved.⁶ Endovascular treatment is therefore a favorable alternative for these subgroups. Fang et al⁶ reported on the use of stent-assisted coiling in the treatment of 21 patients with 42 tandem aneurysms, most of which were located within the ICA or middle cerebral artery; 1 patient had tandem aneurysms located within the posterior circulation.⁶ Of these, 57.1% of patients presented with a ruptured aneurysm. At last angiographic follow-up (mean, 25.4 months), complete occlusion was achieved in 76.5%. There were no symptomatic thromboembolic complications. The authors concluded that stent-assisted coiling may have an advantage over the PED in the treatment of ruptured and posterior circulation aneurysms. However, there was no direct comparison within the study.

Lin et al⁸ reported on endovascular treatment of 13 patients with 28 tandem aneurysms. In 1 case, the aneurysms were located within the posterior circulation. Seven patients were treated with stent-assisted coiling, while the remaining 6 patients were treated with the PED. At last angiographic follow-up (mean, 20.3 months), complete occlusion was achieved in 90% of PED-

Table 4: Outcome measures

Parameter	Solitary Aneurysm	Tandem Aneurysms	P Value
Length of procedure (median) (range) (min)	69.5 (16–192) ^a	76 (19–194) ^b	.52
PED dimensions (median) (range) (mm)			
PED length	19 (12–35)	20 (6–30)	.42
PED diameter	4 (2.5–5.5)	4 (3.5–5)	.26
Last angiographic follow-up (median) (range) (mo)	12 (1–79) ^c	18 (4.8–51) ^d	.008
Follow-up occlusion rate (No.)			
Complete (100%)	109 (75.1%) ^c	62 (88.6%) ^d	.06
Near-complete (90%–99%)	12 (8.3%)	4 (5.7%)	
Partial (<90%)	24 (16.6%)	4 (5.7%)	
Retreatment (No.)			
Endovascular	7 (4.9%)	4 (5.7%)	.81
Posttreatment mRS (No.)			
0–2	169 (98.8%) ^e	32 (97%) ^f	.42
3–5	2 (1.2%)	1 (3%)	
Follow-up mRS (No.)			
Improved	47 (27.5%) ^e	9 (27.3%) ^f	.33
No change	112 (65.5)	24 (72.7%)	
Worsened	12 (7%)	0	
Neurologic complications (No.)			
Symptomatic thromboembolic	5 (2.7%)	3 (8.8%)	.08
Permanent	3 (1.6%)	1 (2.9%)	.60
Symptomatic hemorrhagic	2 (1.1%)	1 (2.9%)	.39

^a Data are missing for 32 procedures.

^b Data are missing for 15 procedures.

^c Data are missing for 39 aneurysms.

^d Data are missing for 8 aneurysms.

^e Data are missing for 13 procedures.

^f Data are missing for 1 procedure.

treated aneurysms compared with 72.7% of those treated with stent-assisted coiling. Two patients (28.6%) treated with stent-assisted coiling required retreatment.

The high rate of complete occlusion following PED placement compared with stent-assisted coiling is likely due to the larger surface area coverage provided by the PED, leading to better reconstruction and endothelialization of the aneurysm neck. The PED can also theoretically induce repair of a dysplastic parent vessel and therefore potentially offer more durable treatment of adjacent tandem intracranial aneurysms.⁹ The PED has also proved effective in small aneurysms,¹³ which often make up the adjacent aneurysms in patients with tandem aneurysms and in whom there is a particularly high risk of rupture when treated with traditional stent-coiling techniques following deployment of the stent. Moreover, in the treatment of tandem aneurysms, the PED is often technically preferred because placement of a single PED can be sufficient to achieve complete occlusion of all aneurysms, compared with stent-assisted coiling, in which each aneurysm has to be catheterized and treated separately.

Hemodynamics of Tandem Aneurysm Occlusion

Mut et al⁹ examined the hemodynamics of tandem aneurysm occlusion following PED placement. They proposed that aneurysms located on the convex side of the parent artery wall have an inflow stream entering the aneurysm through the proximal aspect of the neck, while the aneurysms located in the concave part of the wall have an inflow through the distal aspect. Following PED placement, the aneurysms on the concave side of the parent artery have a larger reduction in aneurysm inflow, mean velocity, shear rate, and wall shear stress and smoother flow patterns, leading to faster occlusion compared with their convexity counterparts. They also

reported that the energy content in the aneurysm (total kinetic energy calculated over the aneurysm sac) at the convex side changed from 30% of the energy of the parent artery to 13%, while in the aneurysm at the concave side, it changed from 18% to approximately 3%. When the energy content (or energy loss) approaches zero, the blood flow is expected to cease with subsequent blood coagulation and obliteration of the aneurysm.

In the present study, the side of the aneurysm orifice in respect to the parent artery geometry had no correlation with complete occlusion because 4 of 8 (50%) aneurysms with incomplete occlusion were located on the concave portion of the parent artery. However, in 5 of 8 (62.5%) cases of incomplete occlusion, the aneurysm was part of a tandem sequence of 2 aneurysms that were separated by at least 1 ICA segment. For example, 1 aneurysm was located in the cavernous segment of the ICA, while the second was located along the ophthalmic segment. Moreover, complete occlusion occurred in the proximal aneurysm in all cases, while the distal aneurysm failed to occlude. In the remaining 3 cases, all aneurysms within the tandem sequence along the ophthalmic segment remained patent. Another factor that may explain the failure to occlude in tandem aneurysms is the size of aneurysm because in 5 of 8 (62.5%) aneurysms, it was the larger aneurysm that failed to occlude. However, due to the limited number of cases, further studies with greater numbers of patients are required to investigate this hypothesis.

Complications

The natural history of tandem aneurysms is not well-understood. Kaminogo et al² reported no significant difference in the rate of acute SAH between single and multiple aneurysms at the time of presentation, which is supported by the present study. Inagawa,¹ on the other hand, reported a positive correlation between the multiplicity of the aneurysms and a risk of aneurysm rupture.

Following endovascular procedures, Lin et al⁸ reported no significant difference in the rate of complications between stent-assisted coiling and the PED for the treatment of tandem aneurysms. However, in their study, the number of PEDs placed for aneurysm treatment was variable. Moreover, no previous study has compared the outcomes following PED placement in the treatment of tandem-versus-solitary aneurysms.

In the present study, symptomatic thromboembolic complications were encountered following 3 procedures (8.8%) for PED placement in the treatment of tandem aneurysms compared with 2.7% in the treatment of solitary aneurysms ($P = .08$). Permanent symptoms (lasting >30 days) as a result of ischemic stroke were encountered in 1.6% and 2.9% of procedures for the treatment of

solitary and tandem aneurysms, respectively ($P = .6$). Although there was a tendency for tandem aneurysms to occur in smokers, smoking per se had no significant correlation with thromboembolic complications.

Limitations

We acknowledge that our study is limited by its retrospective nature. Although the inclusion of multiple institutions improves the generalizability of the findings, it introduces variability in patient management, follow-up protocols, imaging studies, and evaluation of aneurysm occlusion. There was also variation in patient characteristics and aneurysm size between both comparison groups, and only a relatively small number of complications were observed in each group, limiting the power of the study to detect small differences between groups. However, this is the largest comparison of tandem and single aneurysms treated by the PED in the literature, to our knowledge, and there were attempts to control for significant differences between comparison groups during analysis of outcomes.

CONCLUSIONS

Tandem aneurysms of the internal carotid artery can be treated with a single PED with high rates of complete aneurysm occlusion. The higher rates of aneurysm occlusion in the tandem group compared with the solitary group could be confounded by differences in aneurysm size. While there did appear to be a trend toward higher thromboembolic complication rates in the tandem group, this did not reach statistical significance.

Disclosures: Adnan H. Siddiqui—UNRELATED: Board Membership: Intersocietal Accreditation Commission; Consultancy: Codman, Medtronic, Guidepoint Global Consulting, Penumbra, Stryker Neurovascular, MicroVention, W.L. Gore and Associates, Three Rivers Medical Inc, Corindus Inc, Amnis Therapeutics Ltd, CereVasc LLC, Pulsar Vascular, The Stroke Project Inc, Cerebrotech Medical Systems Inc, Rapid Medical, Neuravi, Silk Road Medical, Rebound Therapeutics Corp, Claret Medical Inc, Comments: also Principal Investigator/National Steering Committees: Penumbra: 3D Separator Trial, COMPASS Trial, INVEST Trial; Covidien (now Medtronic): SWIFT PRIME and SWIFT DIRECT Trials; MicroVention: FRED Trial, CONFIDENCE Study; Codman & Shurtleff: LARGE Trial; MUSC: POSITIVE Trial; Stock/Stock Options: StimMed, Valor Medical, Neuro Technology Investors, Cardinal Health, Medina Medical Systems, Buffalo Technology Partners LLC, International Medical Distribution Partners. Elad I. Levy—UNRELATED: Board Membership: Stryker Neurovascular, NeXtGen Biologics, and MEDX, Comments: served on acute ischemic stroke Clinical Advisory Board for Stryker Neurovascular, serve on Advisory Board for NeXtGen Biologics and MEDX; no money; Consultancy: Pulsar Vascular; Payment for Development of Educational Presentations: Covidien, Comments: honorarium for training and lectures; Stock/Stock Options: Intratech Medical Ltd and NeXtGen Biologics, Comments: shareholder/ownership interest; Other: Abbott Vascular, Comments: carotid training sessions for physicians. Ajith J. Thomas—UNRELATED: Consultancy: Stryker Neurovascular, Comments: data safety monitoring board*; Expert Testimony: CRICO, Comments: expert witness, neurovascular. *Money paid to the institution.

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