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Original Article

The use of flow diverters to treat small (≤5 mm) ruptured, saccular aneurysms

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Abstract

Background: There is limited published literature on the use of flow diverting stents (FDS) to treat ruptured intracranial aneurysms in the acute stage. We present our experience of using FDS to treat small (≤5 mm) ruptured aneurysms.

Methods: We retrospectively identified all patients with ≤5 mm ruptured aneurysms treated exclusively with FDS between February 2009 and February 2016. We recorded demographic data, the Hunt and Hess score, aneurysm location and size, therapeutic intervention, immediate angiographic and clinical result, and clinical and radiological follow-up information.

Results: We identified seven patients (four females) with average age 59.8 ± 10 years (range 48–75). The average aneurysm fundus size was 2.7 ± 0.76 mm (range 1–4 mm). The average time from ictus to treatment was 6.3 days (range 1–14 days) and there were no cases of repeat rupture prior to treatment or intraoperative rupture. Angiographic follow-up was available in five patients. At initial follow-up, aneurysms (100%) were completely occluded raymond roy classification 1 (RRC 1). None of the aneurysms re-ruptured following treatment. Clinically, six patients were discharged with good functional outcome modified Rankin Score (mRS ≤2). There were no mortalities.

Conclusion: The use of FDS to treat small, ruptured, saccular aneurysms is feasible; however, the use of FDS should not be considered first-line treatment. Further studies are required to determine the safety and efficacy of the use of FDS in the acute situation.

Key Words: Flow diverter, ruptured aneurysm, subarachnoid haemorrhage

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INTRODUCTION

The introduction of flow diverting stents (FDS) represented a paradigm shift in the way intracranial aneurysms were treated and for the first time a treatment option that allowed reconstruction of the diseased parent artery became available. Although the exact mechanism of action by which flow diverters act is debated, there is a general consensus that initially these devices alter the intra-aneurysmal hemodynamics to promote thrombosis with subsequent formation of neo-intima over the braided stent wires and complete exclusion of the aneurysm from the circulation.[15,21,26] Numerous studies have demonstrated that the devices have an acceptable safety profile and good efficacy.[3-9,12,13,16,20,23,27,29,32,34,38,39,42,43,46,49,51,53-55] The Pipeline for Uncoilable or Failed aneurysms study (PUFS)[3] showed an aneurysm occlusion rate of 73.6% at 6 months and major ipsilateral stroke or neurological death rate of 5.5% whilst the Pipeline embolization device for the Intracranial Treatment of Aneurysms showed a 6-month aneurysm occlusion rate of 93.3% and ischemic stroke risk of 6.5%.[40] The 5-year follow-up data for the PUFS study were recently published and demonstrated good long-term safety with the vast majority of patients having a good clinical outcome.[2] The safe use of these devices requires adequate antiplatelet medication.[22,23,46] Recently, newer devices with surface modifications that are designed to be less thrombogenic have entered the market;[24,25,35] however, clinical experience is limited. Given the delay in complete exclusion of the aneurysm and the need for antiplatelet medication, the uptake of FDS in ruptured intracranial aneurysms has naturally been muted. Nevertheless, several reports have now been published documenting the use of FDS in acutely ruptured saccular, dissecting, fusiform, and blister aneurysms of both the anterior and posterior circulation.[17-19,36,41,52]

In this study, we present our data on the treatment of acutely ruptured, small (≤5 mm), saccular aneurysms with FDS.

METHODS

Patient population

We searched our prospectively maintained database, for patients treated in our institution between February 2009 and February 2016, with ruptured, saccular aneurysms ≤5 mm in maximal size treated with FDS in the acute and early subacute period (≤14 days). Patients treated prior to the acute rupture with clipping, for example, ruptured remnant, were also included. Exclusion criteria included fusiform, blister, and dissecting aneurysms. We excluded aneurysms that were coiled acutely and then treated with flow diversion either during the same hospital admission or at a later date.

For each patient, we recorded demographic data, clinical presentation, aneurysm location, therapeutic intervention, immediate angiographic and clinical result, and clinical and radiological follow-up information.

Endovascular treatment

All treatments were performed under general anesthesia. A single type of flow diverter, the p64 (Phenox, Bochum, Germany), was used in all cases and this was based upon the higher mesh density compared to the Pipeline Embolization Device (PED) (Medtronic, Dublin, Ireland) which is the only other flow diverter available in our department.

Dependent upon the clinical state of the patient, premedication was given either on table or orally at least 3 h prior to the operation for patients able to take oral medications. For patients able to take oral medications, loading doses of aspirin (500 mg) and ticagrelor (180 mg) were given on the morning of the surgery. The effectiveness of the antiplatelet medication was tested using both the VerifyNow (Accumetrics) and Multiplate (Roche) analyzers to ensure adequate anti-aggregation prior to the operation and at least 3 h post-medication. For patients unable to take oral medication prior to the operation, an intravenous bolus dose of weight-adjusted eptifibatide was given on table. Subsequently, loading doses of ticagrelor via NG tube (180 mg) and IV aspirin (500 mg) were given at the end of the procedure. In both situations, the effectiveness of the antiplatelet medication was tested 24-h post-procedure using the VerifyNow and Multiplate analyzers.

The post-procedural antiplatelet regimen consisted of ticagrelor (90 mg twice daily) continued for 12 months following treatment and aspirin (100 mg once daily) continued for life.

The preoperative brain imaging was carefully assessed to determine if an external ventricular drain (EVD) was required or may be required. Signs of obstructive hydrocephalus, intraventricular blood, or evidence of raised intracranial pressure were used as markers to guide the insertion of an EVD. The EVD was inserted prior to the initiation of antiplatelet medication. Following insertion of the EVD, repeat imaging was performed to assess both the positioning of the EVD and to exclude hemorrhage along the EVD tract. Antiplatelet medication was commenced only after hemorrhage following drain insertion had been excluded.

All procedures were performed via the right common femoral route using a 6-Fr access system as standard. All procedures were performed under heparin anticoagulation with a 5000-IU bolus dose at the start of the procedure and subsequent 1000-IU bolus doses every hour to maintain the activated clotting time between 2 and 2.5 times the baseline.

Procedural assessment and follow-up

Patency and flow characteristics within the aneurysm and parent artery were assessed angiographically immediately after placement of the FDS and during follow-up. Follow-up axial imaging, either CT or MRI, were performed prior to the discharge of the patient. A CT angiogram was routinely performed if the patient developed signs or symptoms of delayed cerebral vasospasm.

Procedural follow-up was performed initially at 3–6 months, again at 9–12 months, and then once per year. Standard angiographic projections were used to assess the patency of the vessels and the aneurysms in addition to angiographic projections that repeated those used during the treatment. Aneurysm occlusion was graded as either completely excluded, minor remnant, major remnant, or unchanged (patent) and additionally using the 3-point Raymond–Roy classification.[45]

RESULTS

Population

In total, we identified 320 patients with ruptured aneurysms ≤5 mm in size. We identified seven patients (four females) that met our inclusion and exclusion criteria. The average age of the patients was 59.8 ± 10 years (range 48–75). The average aneurysm fundus size was 2.7 ± 0.76 mm (range 1–4 mm). The average neck width was 2.5 ± 0.5 mm (range 1–5 mm) with average aspect ratio 1.1. The majority of aneurysms were located in the anterior circulation (n = 5) with three aneurysms located in the clinoidal or supraclinoidal segment of the internal carotid artery (ICA), one aneurysm located at the A1/A2 junction, and one aneurysm on the pericallosal artery. In the posterior circulation, one aneurysm was located on the superior cerebellar artery and one aneurysm on the posterior cerebral artery. None of the aneurysms was previously treated.

In terms of clinical presentation, three patients presented with Hunt and Hess grade 1, two patients with Hunt and Hess grade 2, one patient with Hunt and Hess grade 3, and one patient with Hunt and Hess grade 5 subarachnoid hemorrhage. One patient had an EVD inserted and in one patient a lumbar drain was inserted. There were no cases of hemorrhage secondary to drain insertion or following initiation of antiplatelet medication. The results are summarized in Table 1.

Feasibility

Delivery of the flow diverter was feasible in all cases. The p64 was used in all cases. In a single patient, two p64 flow diverters were used. In the remaining six patients, a single FDS was deployed. The average time from ictus to treatment was 6.3 days (range 1–14 days) and there were no cases of repeat rupture prior to treatment. Treatment was significantly delayed in two patients (patient 4 and 7). In patient 4, this was due to unsuccessful surgical attempt at clipping and then the development of vasospasm. In the patient 7, the patient presented in a delayed fashion and initially remained undiagnosed in a nonspecialist hospital.

The use of flow diversion was taken after multidisciplinary team discussion in six cases and based principally around the unfavorable morphology and anatomical configuration of the aneurysm. In all cases, the aneurysms had unfavorable aspect ratios, ≤1.3 in all cases, which would have likely necessitated the use of stent-assisted coiling. Furthermore, given the small size of the aneurysms (2.7 ± 0.75 mm), we felt that catheterization of the aneurysm, without the protection of a balloon, would pose a risk of intraoperative rupture. In one case, patient 4, the patient initially went to surgery. At the time of surgery, the rupture point of the aneurysm was found to be at neck of the aneurysm and therefore clipping of the aneurysm would have involved occlusion of the pericallosal artery. Similarly, because of the rupture point, endovascular coiling was also felt to be high risk.

There were no cases of intraoperative aneurysm rupture and there were no intraoperative complications.

Angiographic and clinical follow-up

Angiographic follow-up was available in five patients. At initial follow-up performed on average at 3.4 months after the procedure, five aneurysms (100%) were completely occluded (RRC 1). In two patients, there is no follow-up angiographic imaging

Table 1: Baseline demographics and aneurysm characteristics

Patient number	Age	Sex	Aneurysm characteristic		Neck width (mm)	Dome height (mm)	Aspect ratio	Previous treatment	Hunt and Hess	EVD inserted
			Location	Laterality						
1	48	Female	ICAophth	Left	2.5	3	1.2	0	2	No
2	66	Female	SCA	Left	3	3	1.0	0	5	Yes
3	75	Female	A1/A2	Right	2	2	1.0	0	2	No
4	63	Female	Pericallosal	Right	3	3	1.0	0	3	No (lumbar)
5	55	Male	PCA	Right	2	2	1.0	0	1	No
6	64	Male	ICAhyp	Right	3	4	1.3	0	1	No
7	48	Male	ICAhyp	Left	2	2	1.0	0	1	No

available [Figures 1 and 2]. All patients had follow-up MRI postoperatively and there was no evidence of new infarction identified on diffusion-weighted imaging.

None of the aneurysms re-ruptured following treatment. Clinically, six patients were discharged with good functional outcome (mRS ≤2), and the remaining patient was discharged with mRS 5, which was her baseline neurological status. There were no mortalities. The results are summarized in Table 2.

DISCUSSION

Stent-assisted coiling is a widely used and accepted treatment option for unruptured intracranial aneurysms; however, the use of stents in the acute situation is generally avoided unless absolutely necessary. The use of stents, either alone or in conjunction with endovascular coiling, in the acute situation is believed to expose patients to an elevated risk of bleeding-related complications if interventions such as the insertion of an EVD are required.[1,10,28,37,47,48] Bodily *et al.*[11] performed a systematic review of the literature to analyze the risks associated with the use of non-FDS with acutely ruptured intracranial aneurysms. They identified 17 articles and 339 patients. They report a total hemorrhagic complication rate of 8% (27/339); however, 9 of these patients were hemorrhage related to the EVD and 12 were intra-procedural rupture of the aneurysm. Similarly, they reported clinically significant thromboembolic events in 6% of cases with available data. Of note, over half of the EVD-related hemorrhagic events came from a single case series.[50] Kung *et al.*[30] performed a retrospective review of 131 patients who had EVD insertion with and without concomitant dual antiplatelet therapy in the setting of acute subarachnoid haemorrhage (SAH). They found that in those patients that required stent-assisted coiling, and hence dual antiplatelet therapy, the rate of symptomatic and radiographic hemorrhage was 32% compared to 14.7% in those that were not on antiplatelet medication. Given the increased risk of hemorrhage, we insert an EVD prior to initiating antiplatelet medication, and if a permanent

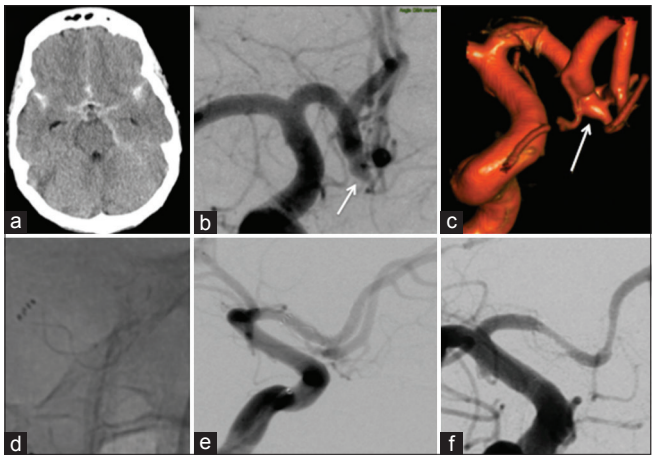

Figure 1: Patient 4 presented with diffuse subarachnoid hemorrhage (a) and a solitary aneurysm of the A1/2 junction [(b and c) white arrows). After an attempted clipping, the patient was referred for endovascular treatment with a single p64 flow diverter (d and e). There were no intraoperative complications and there was no evidence of recurrent hemorrhage. Follow-up angiography at 4 months revealed complete exclusion of the aneurysm and asymptomatic, mild/moderate in stent stenosis (f)

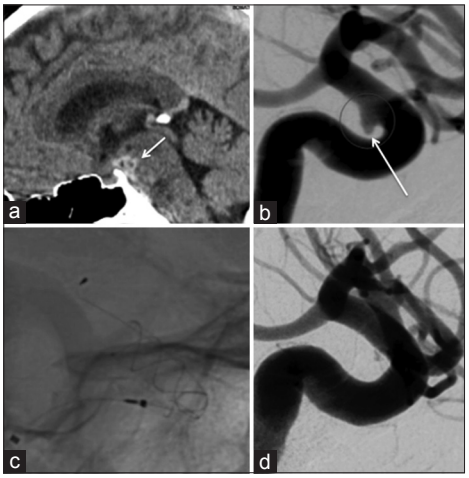

Figure 2: Patient 6 presented with a localized subarachnoid hemorrhage (a, short white arrow) and a solitary aneurysm of the ICA (b, long white arrow). The wide neck would have necessitated stent-assisted coiling, and therefore, flow diversion was thought to represent a safer treatment option (c). Follow-up angiography at 3 months showed virtually complete exclusion of the aneurysm from the circulation (d). There was no evidence of repeat hemorrhage and no clinical or radiological complications following the implantation of the p64 flow diverter

Table 2: Clinical and radiographic outcome data

Patient number	Time to treatment (days)	Number and type of FDS	Adjunctive coiling/surgery	EVD hemorrhage	Procedural complication	mRS	Radiographic outcome (RRC)
1	1	2 × p64	N	NA	0	0	1
2	4	1 × p64	N	N	0	5	NA
3	3	1 × p64	N	NA	0	0	1
4	12	1 × p64	Failed clipping	NA	0	1	1
5	5	1 × p64	N	NA	0	1	NA
6	5	1 × p64	N	NA	0	0	1
7	14	1 × p64	N	NA	0	0	1

FDS: Flow diverting stents; EVD: External ventricular drain; RRC: Raymond roy classification

shunt is required, we usually place the same tract and burr hole as that used for the EVD, a technique that has also been shown to be safe and effective by others.[44] None of our patients suffered a hemorrhage related to the EVD and we believe that this highlights the need to insert the EVD prior to commencing antiplatelet medication.

Several studies have documented the use of FDS in the acute situation,[17,36,41] although the majority of these studies have amalgamated the results from SAH of various different underlying causes, for example, acute dissection, fusiform aneurysm rupture, blister aneurysm, and ruptured saccular aneurysms. In the series by Chalouhi *et al.*,[17] 9/20 aneurysms were small (<5 mm) and 7 of these were very small (≤3 mm). The aneurysms were treated an average of 7.9 days post-rupture (range 0–17 days) which is similar to the treatment time interval seen in our own series. Follow-up data were available for five aneurysms with four showing occlusion, although the timing of the follow-up for these patients was not individually reported. All patients had good clinical outcome (mRS ≤ 1). In the earlier series of McAuliffe and Wenderoth[36] of the 11 patients studied, 3 had saccular aneurysms; however, all were ≥10 mm. Two of the aneurysms were treated with only FDS but one aneurysm (21 mm) was also treated with adjunctive coils. Two of the patients showed complete occlusion at last follow-up and one patient died. More recently, Madaelil *et al.*[33] performed a meta-analysis of ruptured aneurysms treated with FDS. They identified 20 observational studies with 126 patients. The average time to treatment was 9.6 days with approximately three-fourth of patients treated in the acute phase. In 96% of cases, the PED was used and in the remaining 4% of cases, the Silk (Balt Extrusion, Montmercy, France) was used with just under three-fourth of the patients treated solely with FDS. Angiographically, 94% of aneurysms <7 mm treated exclusively with FDS were occluded at follow-up. The average size of the aneurysms treated with FDS alone was 5.6 ± 6.4 mm compared to 10.6 ± 6.4 mm ($P = 0.001$) for those treated with both coils and FDS. In terms of complications, re-rupture of the culprit aneurysm was recorded in six cases with four of these occurring in aneurysms >2 cm. Hemorrhagic complications not related to repeat aneurysm rupture were seen in 5/126 cases, only 2 of which were related to EVD placement.[31,52] A favorable clinical outcome was seen in 88% of cases with aneurysms <7 mm, and in this cohort, the use of FDS alone was associated with a more favorable outcome (91%) than FDS and adjunctive coiling (73%). The authors suggest that FDS represent a viable treatment option for ruptured intracranial aneurysms that are not readily amenable to first-line treatment such as coil embolization or clipping.

When considering the benefits and risks of FDS as a treatment option for small, ruptured aneurysms, it is important to compare with the risks of standard endovascular coiling. These risks relate to the difficulty in obtaining a stable microcatheter position as well as to the perceived increased risk of perforation related to the small, confined space. However, aneurysms smaller than 3 mm are routinely coiled and advances in imaging, increasing operator experience, and the widespread use of adjunctive devices have all assisted in making coiling of these tiny aneurysms feasible. Recently, Brinjikji *et al.*[14] published the results of their own consecutive series with a meta-analysis. They identified 71 consecutive patients with aneurysms ≤3 mm, 47 of whom had unruptured aneurysms with the remainder having ruptured aneurysms. The majority of the aneurysms, both ruptured and unruptured, were located in the anterior circulation with the average size of the aneurysms dome measuring 2.7 ± 0.35 mm, which is virtually identical to the size of the aneurysms in our series. Approximately half of the aneurysms were treated without the need for adjunctive devices. Posttreatment angiography showed that approximately 87% of aneurysms had complete or near complete occlusion. Of the 58 cases with a follow-up angiogram (mean 10.6 months) performed, 91.4% of aneurysms showed complete or near complete occlusion. Intra-procedural hemorrhage occurred in 8.5% of unruptured aneurysms but in 16.7% of ruptured cases. None of these resulted in permanent morbidity or mortality; however, one treated ruptured aneurysm that was incompletely coiled in the acute phase re-ruptured 10 days postoperatively and resulted in fatality. In the meta-analysis, data on 422 aneurysms, including 271 ruptured aneurysms, were analyzed. Overall, 95.3% of aneurysms were completely or nearly completely occluded at the immediate postoperative angiography. The intra-procedural rupture rate for unruptured aneurysms was 5.0% (95% CI, 2.3–10.4%) compared to 10.7% (95% CI, 7.4–15.1%) in the ruptured aneurysms. Morbidity in ruptured cases was 1.8% (95% CI, 0.6–5.4%). The mortality due to intra-procedural rupture in ruptured aneurysms was 3.1% (95% CI, 1.5–6.3%). The risk of early post-procedural hemorrhage for ruptured aneurysms was 2.4% (95% CI, 1.0–6.0%). Therefore, whilst coiling of small aneurysms is possible, it is certainly not without risks and these risks can be significant. This relatively high rate of rupture seems predictable given the technical challenges associated with coiling very small aneurysms, and naturally, the main advantage of FDS in this scenario is that one does not need to enter the ruptured aneurysm.

The introduction of surface-modified FDS with the requirement for only a single antiplatelet medication may prove particularly useful in the acute situation. We are aware of only a single publication documenting the use of these new devices in an acutely ruptured fusiform aneurysm.[25] In this case, aspirin 325 mg was given 2 h prior to the procedure, and prior to commencement of

aspirin, an EVD was inserted. The fusiform aneurysm of the V4 segment of the right vertebral artery was treated using a combination of coils and two Pipeline Shield devices (Medtronic, Massachusetts, USA). Although there were no intraoperative complications, the stent construct was thrombosed at 10-day follow-up angiography and antiplatelet testing done at this time revealed an inadequate response to the maintenance dose of aspirin (81 mg). Therefore, whilst these devices may prove useful in the future, caution is still required.

The retrospective design and small numbers limit our study. It is a single-center study and all the aneurysms were treated with a single type of FDS; extrapolation of these results to other types of FDS may not be feasible. Although we focused our analysis on small aneurysms, the technique could be used for larger aneurysms; however, again the applicability of our results is difficult to determine. Furthermore, as all the aneurysms are saccular, we are unsure of the applicability of the technique to fusiform aneurysms or to blister aneurysms.

CONCLUSION

The use of FDS to treat small, ruptured, saccular aneurysms is feasible, and in our small series, we achieved reasonable radiographic and clinical outcomes with no cases of re-rupture. Although the use of FDS should not be considered first-line treatment, it represents a potential alternative treatment option when standard endovascular coiling or neurosurgery may not be feasible.

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Conflicts of interest
PB and MAP serve as proctors and consultant for Phenox. HH is share holder and co-founder of Phenox.

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