ORIGINAL RESEARCH

Safety and efficacy of the Derivo Embolization Device for the treatment of ruptured intracranial aneurysms

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ABSTRACT

Background The Derivo Embolization Device (DED) is a novel flow diverter with advanced X-ray visibility, potentially lower thrombogenicity, and an improved delivery system.

Objective To evaluate the safety and efficacy of the DED for emergency treatment of ruptured intracranial aneurysms.

Methods Between February 2016 and March 2018, 10 patients (median age 54.5 years, seven women) with 11 aneurysms were treated with the DED at three neurovascular centers. Procedural details, complications, morbidity, and aneurysm occlusion (O'Kelly-Marotta scale, OKM) were retrospectively reviewed.

Results Among 11 aneurysms treated, there were nine anterior circulation and two posterior circulation aneurysms. Aneurysm morphology was saccular in four cases, dissecting in three, blister-like in three, and fusiform in one. In each case, a single DED was implanted and deployment was technically successful without exception. Adjunctive coiling was performed in two aneurysms. We observed one in-stent thrombosis, presumably due to low response to clopidogrel 4 days after the procedure, which remained with a mild hemiparesis after aspiration thrombectomy. No further thromboembolic or hemorrhagic events occurred. Favorable outcome (modified Rankin scale score ≤2) at last follow-up was achieved in all patients. Among 10 aneurysms available for angiographic follow-up, complete aneurysm occlusion (OKM D) was obtained in nine cases (90.0%).

Conclusions In this pilot study, endovascular treatment of ruptured intracranial aneurysms with the DED was feasible and not associated with any incidence of rebleeding. Larger series with longer follow-up are warranted to reach a definite conclusion about this device.

INTRODUCTION

Endovascular flow diversion has rapidly become a cutting-edge treatment for a broad range of unruptured intracranial aneurysms (UIAs).[1] In particular, flow diverter devices (FDDs) have shown huge advantages in the treatment of complex aneurysms, such as wide-necked, large or fusiform aneurysms, which are otherwise difficult to treat by conventional endovascular or surgical means.[2 3] Owing to the high occlusion rates and acceptable morbidity rates of FDDs,[4] the indication for their use is continuously expanding.[5]

However, there are still concerns about using FDDs in the acute phase of aneurysmal subarachnoid hemorrhage (SAH). One problem of FDDs is that they cannot provide immediate aneurysm occlusion, thus aneurysms are at risk of rebleeding during the latency period until complete occlusion is achieved.[6] Moreover, the need for dual antiplatelet therapy (eg, aspirin + clopidogrel) may complicate any additional intracranial procedures required during the management of SAH. Owing to these limitations, flow diverter treatment has been mainly restricted to ruptured intracranial aneurysms (RIAs), such as dissecting, giant, fusiform or blister-like aneurysms, which are morphologically challenging for conventional endovascular and surgical methods.[7–9]

Since the approval of the Pipeline embolization device (PED, Covidien, Mansfield, Massachusetts, USA) by the Food and Drug Administration in 2008, FDDs have been continuously refined and new FDDs have been introduced that deal with the limitations of first-generation devices. Some second-generation FDDs, such as the Pipeline Flex with Shield technology, exhibit a surface finishing with potentially reduced thrombogenicity.[10] However, data on the efficacy and safety of modern FDDs in patients with SAH are scarce.[11 12]

The Acandis Derivo Embolization Device (DED, Acandis, Pforzheim, Germany) is a new self-expandable FDD composed of 48 nitinol composite wires with a radiopaque platinum core and three additional platinum–iridium markers at both ends to enhance its visibility on X-ray imaging.[13] Moreover, the DED is provided with a thin surface layer of titanium oxides and oxynitrides. This is supposed to reduce friction during delivery, leading to potentially lower thrombogenicity of the device.[14 15] Further features of the DED include an improved delivery system and a flexible structure, which enables subtotal resheathing and repositioning. While treatment of UIAs with the DED yielded promising results, its use for RIAs has not yet been the focus of research.[13 16]

The objective of this multicenter study was to report our initial experience with the DED for the treatment of RIAs. We aimed to evaluate the safety and efficacy of this device during the acute phase of SAH and to report short- and mid-term aneurysm occlusion rates.

METHODS

This is a retrospective analysis of all patients treated with the DED during the acute phase of SAH at

three neurovascular, tertiary care centers in Germany between February 2016 and March 2018. In accordance with the institutional guidelines, no ethics committee approval was required for this retrospective observational study.

Data collection

The imaging and patient data were blinded and independently reviewed by three experienced consultant neurointerventionalists (CK, FD, BK). Discrepancies were resolved by consensus. Patient characteristics, such as age, sex, and World Federation of Neurosurgeons (WFNS) grade, were obtained from the medical charts. The conventional Fisher scale (1, no SAH; 2, thin layer of blood <1 mm; 3, blood clots >1 mm; 4, intracranial or intraventricular hemorrhage) was employed to assess the extent of hemorrhage. Aneurysm characteristics were evaluated by conventional four-vessel digital subtraction angiography (DSA) with three-dimensional rotational angiography. The aneurysm size was defined as the largest diameter of the aneurysm dome. Aneurysm morphology was classified as saccular, dissecting, blister-like, and mycotic.

Interventional procedure

The procedures were performed via a transfemoral access with the patient under general anesthesia. The standard approach was introducing an 8F guiding catheter through a short femoral sheath into the internal carotid artery or a 6F guiding catheter into the vertebral artery, respectively. In the anterior circulation, a triaxial approach was attempted using an intermediate catheter (Navien 058, Medtronic, Irvine, California, USA or Sofia Plus, Microvention, Tustin, California, USA). The DED was delivered through a standard 0.027" microcatheter (Headway 27, MicroVention, Tustin, California, USA) in all cases. Decision-making about flow diversion was made on a case-by-case basis in interdisciplinary consensus between vascular neurosurgeons and neurointerventionalists. The main reason for applying flow diversion was a complex aneurysm morphology (eg, blister, dissecting) that would have been challenging to treat by conventional endovascular or surgical methods. All patients were treated within 24 hours after admission to the hospital. The decision for flow diversion and adjunctive endovascular techniques was left to the operator's discretion. Correct vessel wall apposition of the DED was assessed by DSA and non-subtracted images. We considered device deployment to be successful when the aneurysm neck was completely covered by the DED.

The visibility of the DED on DSA images was rated by an ordinal grading scale (0, invisible; 1, poor; 2, fair; 3, good; 4, excellent) as described in table 1.

Table 1 Device visibility during the procedure. The rating scale includes the visibility of the contour and the radiopaque markers at both ends of the Derivo Embolization Device

Rating (visibility)	Contour	Radiopaque markers
0 (invisible)	Invisible	Invisible
1 (poor)	Invisible	Partially visible
2 (fair)	Partially visible	Partially visible
3 (good)	Partially visible	Fully visible
4 (excellent)	Fully visible	Fully visible

Anti-aggregant therapy

All cases in this series were emergencies, so no antiplatelet testing was done before the procedure. The treatment was performed under anti-aggregant therapy with tirofiban (Aggrastat, Merck, West Point, Pennsylvania, USA) continued for 16–24 hours, followed by a loading dose of clopidogrel (300 mg) and aspirin (150 mg). Maintenance dual antiplatelet therapy consists of aspirin (100 mg/day) permanently and clopidogrel (75 mg/day) for 4 months in each case; antiplatelet testing after the procedure was not performed routinely.

Complications and clinical outcome

Procedure-related complications such as thromboembolic and hemorrhagic events were recorded. Major complications were classified as being associated with transient or permanent neurological deficits or death. Functional outcome was evaluated by the modified Rankin Scale (mRS). Unfavorable outcome was defined as mRS score >2 at last follow-up.

Evaluation of aneurysm occlusion

Angiographic follow-up was performed by DSA. The O'Kelly-Marotta (OKM) grading scale for flow diversion was employed to assess aneurysm occlusion: A, total filling (>95%); B, subtotal filling (5–95%); C, entry remnant (<5%) and D, complete occlusion.[17] In line, the extent of intra-aneurysmal contrast stasis was categorized as: 1, no stasis; 2, moderate stasis; 3, significant stasis.

RESULTS

Patient and aneurysm characteristics

Detailed patient and aneurysm characteristics are listed in table 2. A total of 11 patients with SAH were identified who underwent 11 emergency procedures for the treatment of 12 aneurysms. One patient had two blister-like aneurysms located at the ICA terminus, which were treated by a single DED in one session. After exclusion of one patient with a mycotic aneurysm, 10 patients with 11 aneurysms were enrolled into the analysis. The median patient age was 54.5 years and seven patients (70.0%) were female. Three patients presented with WFNS grade 4 or 5 (30.0%) and five patients with a Fisher grade of 4 (50.0%).

Table 2 Baseline patient and aneurysm characteristics

Patient number	WFNS/Fisher grade	Aneurysm location	Aneurysm size (mm)	Aneurysm morphology
1	1/1	ICA paraophthalmic	5.6	Saccular
2	1/2	ICA terminus (two blister aneurysms)	1.3, 1.1	Blister-like
3	4/4	VA	5.2	Dissecting
4	3/2	ICA terminus	5.5	Dissecting
5	1/4	BA	3.6	Dissecting
6	5/4	ICA terminus	2	Blister-like
7	4/3	ICA/SHA	2.7	Saccular
8	1/4	ICA paraophthalmic	2	Saccular
9	1/1	ICA paraophthalmic	7.4	Saccular
10	1/4	ICA paraophthalmic	4.5	Fusiform

BA, basilar artery ; ICA, internal carotid artery ; SHA, superior hypophyseal artery; VA, vertebral artery; WFNS, World Federation of Neurosurgeons grade.

Table 3 Procedural details

Patient number	DED type	Use of coils/ balloon	Visibility	Side branch overstented	Side branch patent at end of procedure	Heparinization	Procedural antiplatelet medication	Immediate occlusion classification (OKM)	Final wall adaptation
1	4.5/20	Coiling	4	Yes	Yes	5000 IE	Tirofiban	D	Very good
2	4.5/25	-	4	Yes	Yes	No	Tirofiban	A3	Very good
3	4.5/25	-	4	Yes	Yes	No	Tirofiban	A1	Very good
4	4.5/25	-	4	Yes	Yes	No	Tirofiban	A2	Very good
5	4/20	-	4	No	NA	No	Tirofiban	B3	Very good
6	4.5/30	Balloon	4	Yes	Yes	No	Tirofiban	B2	Fair
7	4.5/25	-	4	No	NA	No	Tirofiban	A3	Very good
8	4.5/15	-	4	Yes	Yes	3000 IE	Tirofiban	A2	Very good
9	5.0/20	Balloon, coiling	3	Yes	Yes	4000 IE	Tirofiban	C2	Good
10	4.5/25	-	4	Yes	Yes	No	Tirofiban	A2	Very good

DED, Derivo Embolization Device; NA, not applicable; OKM, O'Kelly-Marotta grading scale.

Of the 11 aneurysms, nine were located at the ICA (81.8%), one at the vertebral artery (9.1%) and one at the basilar artery (9.1%) The median aneurysm size was 3.6 mm (range 1.1–7.4 mm). Aneurysm morphology was saccular in four cases (36.4%), dissecting in three (27.3%), blister-like in three (27.3%), and fusiform in one (9.1%).

Treatment

Procedural details are listed in table 3. Device deployment was successful in all cases. All patients were treated with a single DED. Adjunctive coiling was used for two paraophthalmic ICA aneurysms, in which insufficient contrast stasis was expected owing to their comparably large dome diameter (5.6 mm and 7.4 mm, respectively). Secondary balloon angioplasty was employed for two cases to ensure accurate wall apposition of the DED. In the first case, wall adaptation of the DED was only fair and in the second case balloon angioplasty was performed owing to insufficient proximal opening of the DED. Further additional endovascular devices were not used. Artery side branches were overstented in eight (80.0%) cases, whereby all covered side branches remained patent at the end of the procedure.

Three (30.0%) patients received systemic heparinization in addition to tirofiban.

The visibility of the DED during the procedure was rated as 'excellent' in nine cases and 'good' in one, indicating that the contour and the radiopaque markers at the ends were clearly visible on the DSA images.

Immediate angiographic results are presented in table 3. Complete occlusion (OKM D) was achieved in one (9.1%) aneurysm, while the others showed total (OKM A; n=7) or subtotal filling (OKM B+C; n=3). Among the 10 aneurysms with incomplete occlusion, intrasaccular contrast stasis was significant (OKM 3) in four cases, moderate (OKM 2) in five cases, and absent (OKM 1) in one. Of three aneurysms available for short-term angiographic follow-up (<14 days), all showed progressive aneurysm thrombosis and occlusion proceeding from OKM A or B to OKM D, respectively.

Illustrative cases of aneurysm treatment with the DED are presented in figures 1 and 2.

Complications and clinical outcome

Complications and clinical outcome are listed in table 4. Periprocedural complications occurred in two cases, representing a complication rate of 20.0%. The first patient was treated for a RIA (2 mm) in the ophthalmic segment of the internal carotid artery (ICA) and developed acute right-sided hemiparesis and aphasia 4 days after the procedure. A control angiography showed an in-stent thrombosis. Subsequently, aspiration thrombectomy was performed. After the procedure, the symptoms improved and the patient was discharged with a mild persistent hemiparesis (mRS score 1). Platelet inhibition testing was performed and the patient was found to be a clopidogrel low responder. In consequence, clopidogrel was replaced by prasugrel.

The second patient had a chemotoxic reaction to the contrast agent but recovered fully without clinical sequelae.

All patients survived and attained a favorable outcome at discharge. During the cumulative follow-up period of 6 patient years, we observed no further complications such as delayed ischemic or hemorrhagic events.

Angiographic follow-up

A total of 9 (90.0%) patients with 10 treated aneurysms were available for angiographic follow-up at a median of 223 days (range 12–603 days). Complete occlusion (OKM D) was achieved in nine aneurysms (90.0%). One aneurysm showed incomplete occlusion (OKM A3) 17 days after the procedure and was subjected to further angiographic follow-up. Furthermore, all artery side branches (7/7) covered by the DED were patent on angiographic follow-up imaging. Individual angiographic outcome is presented in table 4.

DISCUSSION

In this pilot study, endovascular treatment of RIAs with the DED was feasible and there was no incidence of rebleeding or major ischemic stroke. Moreover, the results indicate a reliable progression of aneurysm thrombosis in an acceptable time period and we achieved a high rate of complete aneurysm occlusion at mid-term follow-up.

In this study, we evaluated 10 patients with SAH who were treated with the DED for 11 RIAs. Except for one, all aneurysms were <7 mm and considered to be small. Similar to previous reports on FDDs dealing with aneurysm treatment in the setting of acute SAH, we predominantly used the DED for blister-like and dissecting aneurysms.[7 8] These aneurysm types are anatomically challenging for both conventional coiling and microsurgical clipping and might have otherwise required deconstructive techniques such as parent artery occlusion. In this context, we expected that the reconstructive flow diversion technique

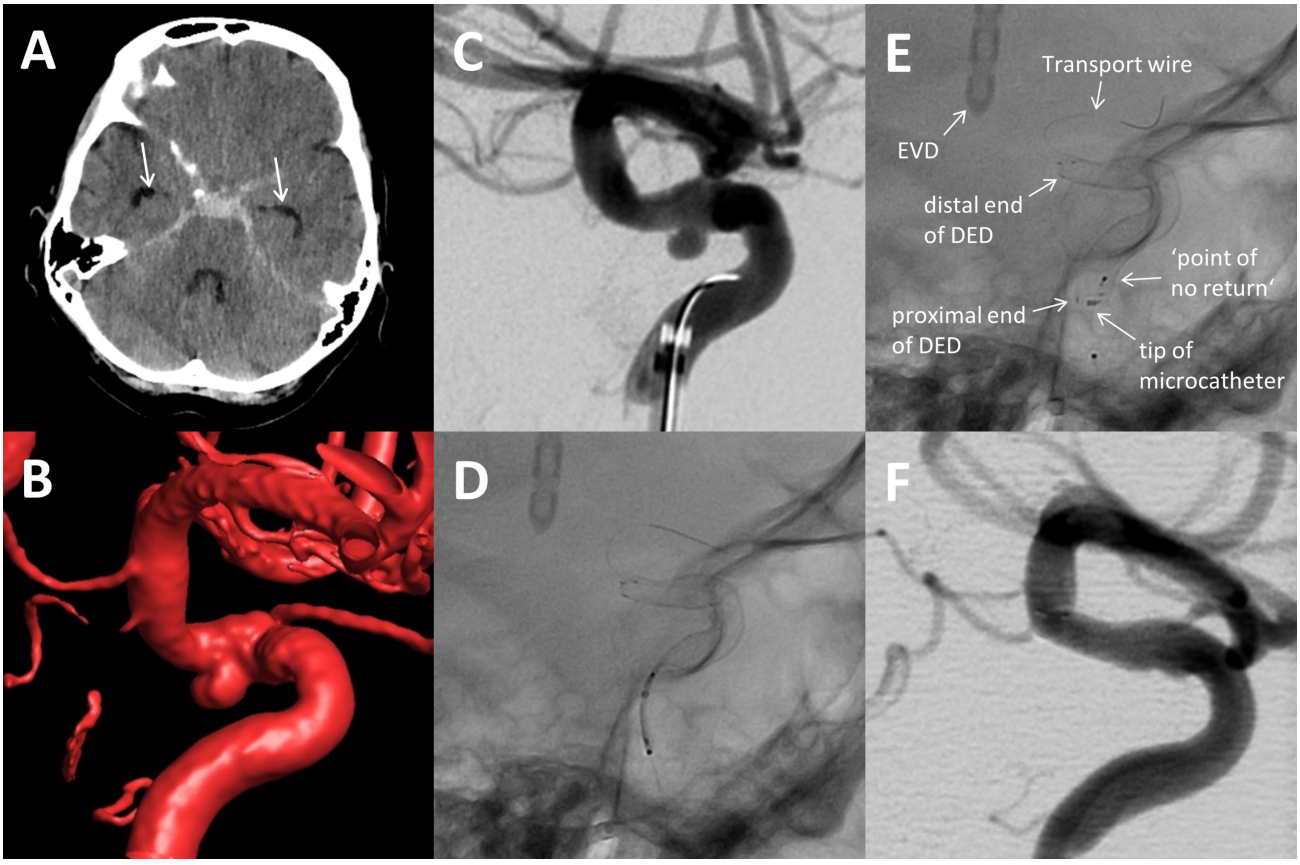

Figure 1 Native cerebral CT shows basal subarachnoid hemorrhage with blood in the Sylvian fissure and initiating hydrocephalus (arrows) (A). Three-dimensional reconstruction and DSA depict a lobulated superior hypophyseal artery aneurysm of the right internal carotid artery (2.7 mm) (B,C). Owing to irregular aneurysm shape and the extent of subarachnoid hemorrhage, we could not exclude the possibility of aneurysm rupture and a decision for aneurysm treatment was made. Unsubtracted DSA images during Derivo Embolization Device (DED) placement reveal favorable visibility of the device during delivery (D, E). DSA immediately after DED placement shows persistent total aneurysm filling (not shown). At 10-month follow-up, DSA reveals complete occlusion of the aneurysm (F). EVD, external ventricular drain.

might confer an advantage for these patients. Moreover, we treated four saccular aneurysms that would have also been accessible by stent-assisted coiling. Owing to unfavorable aneurysm geometry with wide necks and low dome/neck ratio, jailing of a microcatheter before stent deployment or—as an alternative—probing the aneurysm lumen with a microcatheter through the stent interstices to ultimately coil the aneurysm, appeared to be more challenging than implanting a flow diverter. Furthermore, since both techniques require antiplatelets and as there is, at least in scheduled cases, growing evidence that flow diversion might provide higher complete occlusion rates than, and similar morbidity to, stent-assisted coiling,[18] flow diverter therapy was favored by the performing neurointerventionalists.

In our series, the complication rate was 20.0%. We observed one symptomatic in-stent thrombosis in one patient, presumably due to low response to clopidogrel. After aspiration thrombectomy, the patient could be discharged with minor persistent morbidity (mRS score 1). Further thromboembolic or hemorrhagic events did not occur and no procedure-related deaths were seen. Overall, favorable outcome (mRS score ≤2) was achieved in all patients. These safety findings are consistent with previous studies on flow diversion for RIAs. Lin *et al* reported a multicenter study with 26 patients with SAH treated with the PED and reported a periprocedural complication rate of 19.2%, and 20 (76.9%) patients achieved favorable outcome.[8] Three deaths occurred, of which two were procedure related (one rebleeding and one ischemic stroke). Cruz *et al* reported 4 (20%) procedure-related complications in their series on 20 patients with SAH treated with the PED, with one patient dying owing to recurrent hemorrhage.[9] In a previous study by our group of 15 patients with ruptured dissecting aneurysms, we had three complications (20%), which were associated with difficult placement of the PED and required implantation of additional devices.[7] These results collectively suggest that flow diversion for RIAs with anatomically challenging anatomy may be reasonably safe and clinical outcome is comparable to that of other studies on patients with SAH treated with conventional endovascular methods.[19]

The relatively rigid and inflexible structure of first-generation FDDs can make device deployment difficult and may lead to device misplacement. Some authors reported adverse events, which occurred owing to stent misplacement and the subsequent implantation of additional devices.[8] Data suggest that the implantation of multiple devices for each aneurysm is associated with an increased risk of perforator infarction, which may explain these adverse events.[20] In order to minimize the risk of perforator infarction, we attempted to treat the aneurysms with a single DED. This was successful in all cases. In comparison, the percentage of aneurysms treated with multiple devices was reported to be around 35% when using the first-generation PED.[21] By using the DED, all covered side branches were patent at the end of the procedure and at angiographic follow-up. In contrast, previous studies on the PED and other FDDs reported side-branch occlusion rates of approximately 20%.[22]

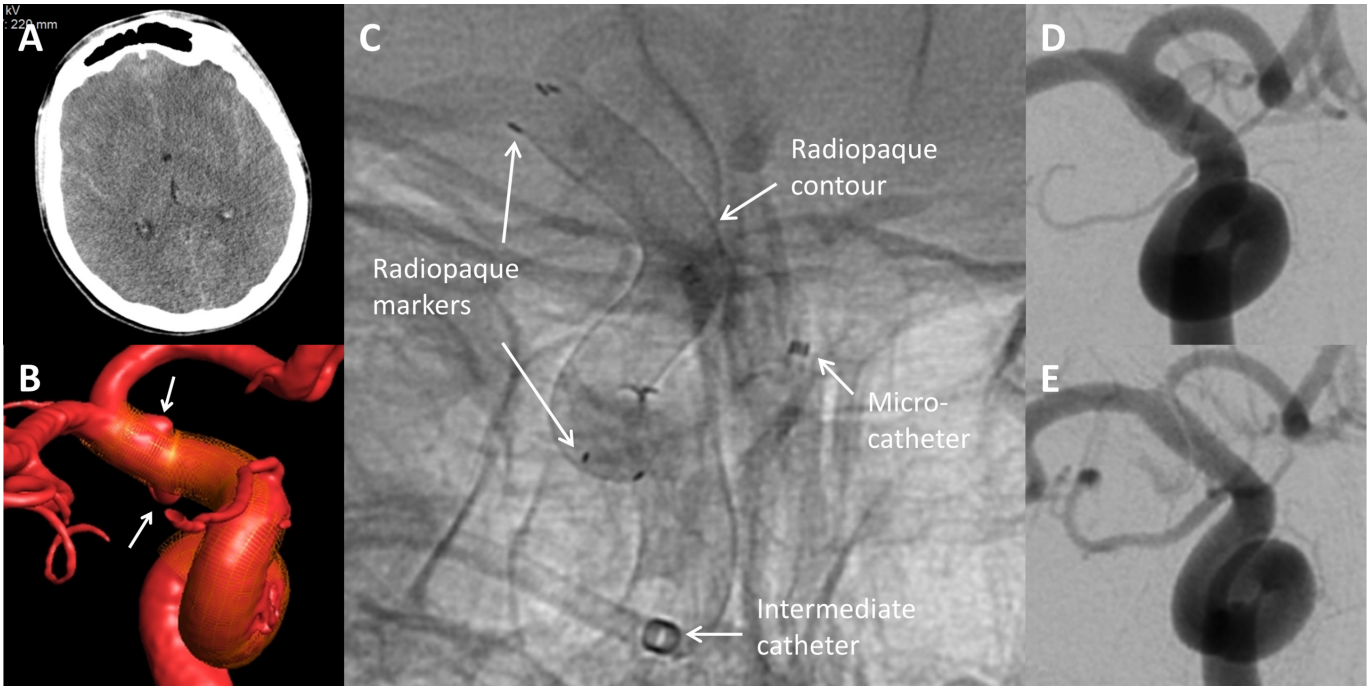

Figure 2 A middle-aged patient presented with basal subarachnoid hemorrhage (A). Three-dimensional rotational angiography reveals two blister aneurysms (arrows) of the terminal segment of the right internal carotid artery (ICA), represented by two contour irregularities of the vessel wall (B). The blister aneurysms exhibited an unfavorable configuration for coiling and microsurgical clipping. A Derivo Embolization Device (DED) was placed within the ICA covering the affected segment. The unsubtracted images during DED placement show the superior visibility of the device contour and the three radiopaque markers at both ends (C). Digital subtraction angiograms before the procedure (D) and at 6-month follow-up show a complete aneurysm occlusion, whereas the covered side branch remained patent (E).

These differences may be attributed to some of the unique features of the DED. The DED has a flexible, self-expandable structure, which enables a subtotal resheathing and repositioning of the device in cases of misplacement. In our experience, adjustment of the device position could be achieved smoothly and without occurrence of adverse events. Moreover, the DED has favorable visibility under fluoroscopy in comparison with conventional stents and FDDs, which was perceived as a safety benefit. Finally, the DED is available in lengths up to 50 mm, which might reduce the number of devices per aneurysm.

Table 4 Adverse events, clinical and angiographic outcome at last follow-up

Patient number	Procedure-related complications	mRS score at last FU	Angiographic FU (OKM)	FU period (days)
1	No	0	D	173
2	No	0	D	603
3	No	2	D	288
4	No	0	D	371
5	No	0	D	174
6	No	0	D	12
7	No	0	D	311
8	Yes, in-stent thrombosis, low clopidogrel response, aspiration thrombectomy, persistent mild hemiparesis	1	D	223
9	Yes, insufficient proximal device opening, balloon angioplasty, chemotoxic contrast reaction, recovered without permanent sequelae	0	-	-
10	No	0	A3	17

FU, follow-up; mRS, modified Rankin scale; OKM, O'Kelly-Marotta grading scale.

A potential drawback of flow diverter treatment for RIAs is that an immediate aneurysm occlusion is not necessarily provided. This might bear the risk of recurrent hemorrhage during the latency period until complete aneurysm occlusion is attained. Since rebleeding is associated with poor functional outcome and high rates of mortality,[23] an early treatment of the aneurysm achieving complete occlusion is advocated. To mitigate this risk, some authors recommend flow diversion in conjunction with coiling to ensure immediate occlusion of the ruptured aneurysm dome.[8] In our series, 9 of 11 aneurysms were treated by flow diversion only. No periprocedural hemorrhagic events occurred and rebleeding was excluded in all patients by CT within 24 hours after the procedure and during follow-up. Based on our still limited experience, treatment of RIAs with the DED without adjunctive coiling is feasible and appears to be reasonably safe; however, these results need to be verified by larger series. In our study, immediate aneurysm occlusion was achieved in 9.1%, which is considerably lower than with conventional endovascular or surgical methods,[19] but is comparable with other series on flow diverter treatment.[11] However, among nine aneurysms with incomplete occlusion, immediate intra-aneurysmal contrast stasis was achieved in all cases. Moreover, in three patients available for short-term follow-up within 14 days after aneurysm treatment, complete aneurysm occlusion was seen, indicating a rapid progression of intrasaccular thrombosis.

The angiographic follow-up results at a median of 223 days showed complete aneurysm occlusion (OKM D) in all cases but one. The aneurysm with incomplete occlusion at 17 days after the procedure showed significant contrast stasis within the

aneurysm cavity (OKM A3) and was subjected to further angiographic follow-up. These angiographic findings confirm the high rates of complete aneurysm occlusion at mid- and long-term follow-up reported by previous studies on FDDs.[24]

Another limitation of flow diversion is the need for anti-aggregant therapy to prevent thromboembolic events. In general, anticoagulant therapy should be avoided during the acute phase of SAH, as it might increase the risk of rebleeding and it complicates intracranial surgical procedures which might be necessary during the acute phase of SAH.

While dual antiplatelet medication (eg, aspirin + clopidogrel) is a well-established standard regimen after elective flow diverter treatment of UIAs, the optimal anti-aggregant therapy for flow diversion of RIAs remains unclear. Aspirin monotherapy as standard of care would be a considerable advancement for flow diverter treatment. However, we found an in-stent thrombosis in a patient without adequate response to clopidogrel, which indicates that aspirin monotherapy does not appear to be a sufficient treatment, even in this new generation of flow diverters.

The conventional dual antiplatelet regimen for flow diverter treatment of RIAs is a loading dose of aspirin and clopidogrel 2–6 hours before the treatment.[8] An alternative approach consists of a maintenance infusion of tirofiban starting immediately after stent deployment and a periprocedural loading with aspirin and clopidogrel.[25 26] At our institutions we adopt a similar protocol, but we continue the tirofiban infusion for 16–24 hours after the procedure and start loading the patients with double antiplatelet medication afterwards. Some of the advantages of tirofiban include its acceptable safety profile and short half-life (2–4 hours). Hence, its effects are fully reversible within 3 hours after stopping the infusion.[27] In comparison, platelet dysfunction lasts for 5–7 days after administration of aspirin and clopidogrel. In our series, the antiplatelet regimen used was not associated with any case of intraprocedural thrombus formation or severe rebleeding during the procedure. For these reasons, this protocol might be a valuable alternative for stent implantation in acute SAH.

A further explanation for the potentially lowered thrombogenicity of the DED may be related to its thin blueish surface layer of oxides and oxynitrides (BlueXide), which reduces the friction during delivery of the device.[13] Preclinical studies indicated a reduced thrombogenic potential of the DED.[14 15] However, clinical evidence is still lacking and 'real-life' evaluation of thrombogenicity needs to be the subject of further research.

Limitations

The limitations of this study are mainly related to its retrospective design and the small number of patients enrolled. The short follow-up periods and the absence of a control group are further limitations. Since we predominantly treated small RIAs, the safety and efficacy of the DED for larger aneurysms remains unclear and needs to be further evaluated. Another limitation is that aneurysm occlusion was not determined by a core laboratory, which might bias interpretation of the angiographic results.[28] To reduce this potential bias, at least in part, all angiographic images were assessed blinded and independently by three experienced consultant neurointerventionalists (CK, FD, BK). Discrepancies were resolved by consensus.

CONCLUSIONS

In our small series we showed that the DED might be a feasible and safe option for complex RIAs that are difficult to treat by conventional endovascular or surgical methods. Larger studies with long-term follow-up are warranted to define the long-term safety and occlusion rates of this device.

Contributors BK, BT, JB, MS, RF, FD, and CK acquired the data. CK and LG developed the project, analyzed the data, and drafted the manuscript. All authors revised the paper critically for important intellectual content and provided final approval of the version published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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