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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - ANEURYSM

Long-term results of flow diversion in the treatment of intracranial aneurysms: a retrospective data analysis of a single center

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Abstract

Purpose Endovascular techniques are frequently used for the treatment of intracranial aneurysms and flow diverter stents are relatively new and important devices in this field. The aim of our study is to report long-term follow-up results of flow diversion treatment.

Methods We retrospectively examined angiographic images and clinical reports of 133 patients (female, 112 [84%]; mean age, 46.3 years [range, 12–70 years]) who were treated with flow diverters between 2008 and 2013 and were followed up radiologically at least 1 year. The aneurysms treated with flow diverters were assessed according to technical problems, stent patency, residual filling, re-growth, and occlusion status, and the patients were assessed according to morbidity and mortality.

Results Except for ten patients, one aneurysm was treated per patient. Median duration of the follow-up was 927 days. Total occlusion rates in angiographic follow-up were found 76.2% for the sixth-month, 86.7% for the first-year, 93.6% for the third-year, 94.2% for the fifth-year, and 90.2% for entire follow-up period. Nine stent morphology changes were observed in the angiographic controls. Overall mortality and morbidity rates were 3.7% and 4.3%, respectively.

Conclusion Despite technical difficulties and delayed hemorrhages, flow diverter stents are effective tools for the treatment of challenging aneurysms in the long run. Nonetheless, long-term results of flow diversion treatment must be evaluated hemodynamically and clinically in multicenter studies.

Keywords Endovascular treatment · Aneurysm · Flow diversion · Stent

Introduction

The use of endovascular methods has been remarkably increased in recent years and is considered the first choice in the treatment of intracranial aneurysms [6, 18, 20]. Although endovascular treatment with coil embolization can be performed successfully in small and non-complex aneurysms, complete occlusion of large (> 10 mm) and giant (> 25 mm) intracranial aneurysms can be achieved at low rates, 40% and 26%, respectively [19]. As the recurrence and re-bleeding are associated with the residual filling in the treated aneurysms, ensuring the total occlusion is very important [10]. Therefore, flow-diverting devices have been developed to provide vascular remodeling. Without aiming to fill the aneurysmal sac, these devices are designed to direct the vascular flow to the parent artery and constitute the skeleton of endothelial reconstruction resulting in secondary thrombosis that leads to subsequent shrinkage of aneurysmal sac [8, 26, 27]. Theoretically, preventing recanalization of the aneurysm can ensure the long-term stable hemodynamic environment.

There are several studies in the literature regarding the early and mid-term results of flow diversion, in which promising results have been reported as well as technical difficulties and procedural complications such as delayed hemorrhage, thromboembolic events, in-stent stenosis, and parent artery occlusion [5, 16, 22–26]. Long-term clinical and radiological

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outcomes are required to improve treatment success, to avoid technical difficulties and complications.

In this study, we aimed to evaluate the long-term outcomes of flow diversion treatment.

Materials and methods

Ethics

The retrospective study was approved by our institutional ethics committee and carried out according to the requirements of the Declaration of Helsinki. All patients gave written informed consent to angiographic procedures and use of imaging data.

Patient population

A total of 161 patients underwent flow diverter stent treatment in the interventional neuroradiology department of Cerrahpasa Medical Faculty between May 2008 and November 2013. Only the patients with at least 1-year clinical and radiological follow-up were included in this study, which resulted in a total of 133 patients with 143 aneurysms. In addition, third-year and fifth-year follow-up data were available in 105 and 83 patients with 110 and 87 aneurysms, respectively. Figure 1 summarizes the number of patients and aneurysms in different time points.

Overall, 99 SILK stents, 11 Pipeline embolization device (PED), and 39 Flow Re-direction Endoluminal Devices (FRED) were used. Some of the patients' early, short-term, and mid-term results (SILK stent, 55 patients with 63 aneurysms; FRED 33 patients with 37 aneurysms) were previously reported in authors' other papers [12, 25]. But the focus of this study is the long-term results.

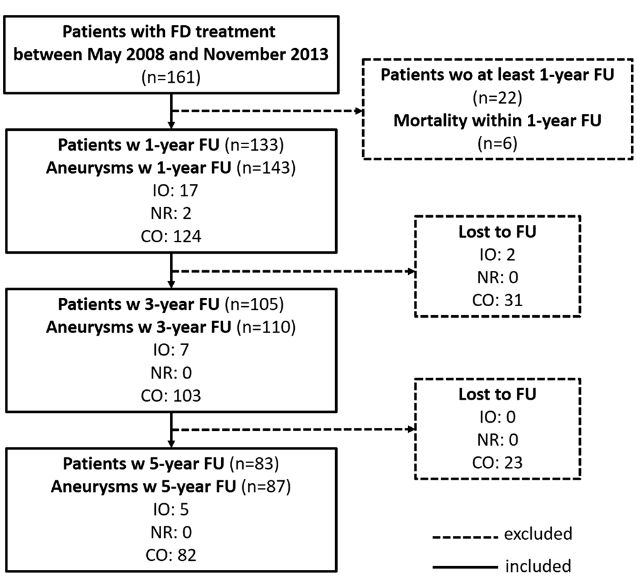

Fig. 1 Flow chart shows the number of patients included and further follow-up details. *WO* without, *W* with, *FD* flow diverter, *FU* follow-up, *IO* incomplete occlusion, *NR* neck remnant, *CO* complete occlusion

Indications of flow diversion treatment

Giant intracranial aneurysms, especially those with a wide neck (> 4 mm) or fusiform shape, are among the most demanding vascular lesions to treat and are common indications for flow diversion treatment. Other indications include aneurysms on dysplastic parent artery, ones with mass effect, small aneurysms (< 2 mm) that are seldom treatable with surgery or conventional endovascular techniques, and dissecting aneurysms.

Pre-treatment and post-treatment medication

Seventy-five milligrams of clopidogrel and 100 mg of aspirin were administered orally for at least 5 days before the procedure. If not received before, the treatment was given orally in the form of a loading dose of 300 mg of clopidogrel and 300 mg of aspirin on the day of the procedure. Of note, patients presented with subarachnoid hemorrhage prior to flow diverter treatment were loaded with 300 mg clopidogrel and 300 mg aspirin immediately before the treatment. Platelet function inhibition in the patients was confirmed by collagen ADP resistivity test; patients with platelet inhibition rate between 40 and 70% were treated with a flow diverter stent. However, for patients whose platelet inhibition rate could not reach 40%, aspirin dose was increased to 300 mg/day. In patients who still failed to maintain the appropriate platelet inhibition rate, in addition to 300 mg/day aspirin, the clopidogrel dose was doubled (150 mg/day) or clopidogrel exchanged for ticlopidine (250 mg 2×/day).

In all patients, endovascular treatment was performed after inducing general anesthesia and applying systemic heparinization. Following the placement of the femoral sheath, 5000 IU heparin was administered as intravenous bolus and then as continuous intravenous perfusion to maintain 2–2.5-fold baseline APTT (active partial thromboplastin time) during the procedure.

After the procedure, heparinization was extended to 24 h in all patients, and LMWH (low molecular weight heparin) was administered for the following days. Also, after discharge, it was recommended to take 75 mg clopidogrel/day for at least 6 months and 300 mg/day aspirin permanently.

In cases in which total aneurysm occlusion cannot be achieved, clopidogrel was discontinued after sixth month and aspirin was reduced to 100 mg at 1 year.

Flow diverter stent technique

All flow diverter stent implantations were performed by at least two senior neuroradiologists (CI., NK., and OK.) on

Philips Integris Allura and Allura Xper FD 20/20 Biplane Angiography (Philips Medical Systems, Netherland).

Unilateral femoral access was used in all patients. After obtaining the appropriate study projection for the aneurysm, that is to be treated, a guide catheter was placed for intracranial access to the relevant vessel segment. Following this, the related microcatheter-microguide system included in the flow diverter stent system was opened after passing the aneurysm segment to cover the aneurysm neck. Since 2010, in all cases, stent apposition to the vessel wall was scanned with flat-panel detector C-arm CT angiography (Philips Healthcare) in neuroangiography suite in addition to regular angiographic images. When necessary, a second stent was implanted, or balloon angioplasty was performed to ensure a satisfactory stent apposition to the vessel wall. All patients underwent control angiography, and the procedure was terminated.

Post-treatment follow-up

After treatment, angiograms were obtained immediately in anteroposterior, lateral, and working positions. The patients were then transferred to the neurological intensive care unit and closely monitored for fluid balance, blood pressure, and neurological status.

On post-procedural day 1, control angiogram was performed. In suitable patients, closure devices were used for groin punctures.

At our institution, a standard follow-up protocol was used: (i), at first month, neurological examination and MRI scan; (ii), at third and sixth months, flat-panel detector C-arm CT angiography; (iii), at 12th month, digital subtraction angiography (DSA) and flat-panel detector C-arm CT angiography were performed, and the results were evaluated by at least two senior neuroradiologists.

The cases, in which total aneurysm occlusion was detected 1 year after treatment, were followed up by annual clinical examination and depending on the findings, appropriate radiological examinations (DSA, MRI, MR-angiography, CT, or flat-panel detector C-arm CT angiography) were performed when necessary. If the aneurysm is still not completely occluded after 1 year, annual MR angiographic imaging was performed. Control DSA or flat-panel detector C-arm CT angiography was planned in all patients at fifth year after flow diversion treatment.

The aneurysms treated with flow diverter stent were assessed according to technical problems, residual filling, stent patency, re-growth, and occlusion status during follow-up period, and the patients were assessed according to morbidity and mortality.

Angiographic outcome evaluation

Follow-up intervals about flow diversion treatment differ in the literature according to the time after procedure and usually defined as follows: early and short-term (0–180 days), mid-term (180–365 days), and long-term (> 1 year) [11].

Aneurysm occlusion status was assessed according to 3-point Raymond-Roy scale.

In-stent stenosis was evaluated based on the minimal luminal diameter and graded as follows: mild (< 50%), moderate (50–75%), or severe (> 75%).

Clinical outcome evaluation

Clinical outcome was evaluated postoperatively, at discharge, at first month, at first year, and annually thereafter using the modified Rankin scale. The primary outcomes assessed were neurological morbidity and mortality.

Results

Patients' demographic data, clinical presentation, and aneurysm characteristics are given in Table 1 and Table 2.

Median follow-up periods after flow diversion treatment were 39 months (12–72 months) for SILK stent (Fig. 2), 36 months (24–48 months) for PED (Fig. 3), and 14 months (12–24 months) for FRED (Fig. 4). The length of follow-up ranged from 382 to 2288 days for all flow diverter stents (median, 31 months [927 days]).

After treatment, complete occlusion rates at sixth-month, first-year, third-year, and fifth-year follow-up period were 76.2% (109/143), 86.7% (124/143), 93.6% (103/110), and 94.2% (82/87), respectively (Fig. 5). Complete occlusion rate at entire follow-up period was found to be 90.2% (129/143).

Successful stent deployment was achieved technically in all procedures. Four of eight patients with bilateral aneurysms were treated with flow diverter stents in the same operation, and the remaining four were stented separately in different sessions. Except for six patients (4.5%), only one flow diverter was placed per aneurysm. In five patients, a second flow diverter stent was implanted telescopically to provide better coverage for entire aneurysm and dysplastic artery. In 20 patients, Leo stents (Balt, Montmorency, France) were implanted in addition to flow diverter stent and in three patients additional coiling was performed to reduce the volume of aneurismal thrombus.

During a total of 149 flow diverter stent implantations, technical complications were observed in 23 (15%) procedures. In 19 (13%) of these, poor apposition of SILK stents to the vessel wall was detected. In all these cases, microballoons were used to obtain optimum stent opening. In three cases, Leo stents were also implanted into the SILK stent to resolve the apposition problem. Other technical problems include detachment of stent in hub of microcatheter ($n = 2$), intra-aneurysmal air bubble ($n = 1$), and partial collapse in inner stent of FRED ($n = 1$). Non-technical procedural

Table 1 Patients' demographic data, clinical presentation, and aneurysm characteristics

	Value (*n*, %)
No. of patients	133
No. of aneurysms	143
Gender	
Female	112 (84%)
Male	21 (16%)
Age at time of treatment	46.3 (range 12–70)
Symptomatic	85 (64%)
Headache	64 (48%)
Cranial nerve deficit	6 (4.5%)
Subarachnoid hemorrhage	6 (4.5%)
Hemifacial spasm	1 (1%)
Dissection	8 (6%)
Asymptomatic	48 (36%)
Incidental	45 (34%)
Re-growth	2 (1.5%)
Prior partial embolization	1 (1%)
Aneurysm morphology	
Saccular	119 (83%)
Wide-necked (> 4 mm)	89 (62%)
Fusiform	9 (6%)
Dissecting	8 (6%)
Blister-like	4 (3%)
Pseudo-aneurysm	3 (2%)
Mean aneurysm diameter	12.1 mm (range, 1.3–49 mm)

complications were observed in 3 (2%) procedures during flow diversion treatment. Bilateral flow diverter stent occlusion was detected in a patient who was treated with placement of an additional stent in the same session. And also, dissection of ICA petrous segment occurred in a patient during the procedure.

Six subarachnoid hemorrhages due to aneurysm rupture were observed postoperatively, and five of these six aneurysm ruptures resulted in mortality. These ruptured aneurysms had

Table 2 Aneurysm location and size

Location	< 7 mm	7–12 mm	13–24 mm	> 24 mm	Total
Intradural ICA	27	32	29	10	98
Extradural ICA	5	3	7	6	21
Vertebrobasilar	3	4	4	2	13
ACA-ACoA	4	3	–	–	7
MCA	1	1	1	1	4

ICA, internal carotid artery; *ACA*, anterior cerebral artery; *ACoA*, anterior communicating artery; *MCA*, middle cerebral artery

no previous history of rupture. All ruptures developed within the first postoperative month. In 5 patients with subarachnoid hemorrhage after flow diverter stent therapy, Glasgow coma scale was found to be 3 and we could not perform any additional intervention. These patients were followed up in the intensive care unit for medical treatment of subarachnoid hemorrhage after external ventricular drainage. The other patient had a mild subarachnoid hemorrhage with Glasgow coma score of 14 on the fifth day following flow diversion. We implanted a second SILK stent telescopically on the right side. The patient was discharged with slight (4/5) left upper extremity paresis.

Four cases of transient clinical worsening due to mass effect after stent implantation were observed. Aneurysm thrombosis was considered as the cause of this temporary clinical deterioration, and these four patients were administered oral steroids (8 mg dexamethasone/day) after having symptoms. At the end of the 1-month follow-up period, clinical findings were completely resolved in all these patients, and neurological examination was found normal.

Seven thromboembolic events occurred in the clinical follow-up period. Six patients experienced persistent morbidity due to stroke, and one patient had a transient ischemic attack.

In the angiographic controls, five in-stent stenoses with SILK stent and four fish mouthing phenomena with FRED were observed. The overall in-stent stenosis rate in control angiographies was 3.7% (5/133), and only one of these five patients was symptomatic. The stenosis in the symptomatic patient was severe (> 75%), but it was reduced below 50% on control angiography with dual antiplatelet therapy (150 mg clopidogrel plus 300 mg aspirin). Of the 133 patients, 4 (3%) showed mild (< 50%) in-stent stenosis with parental artery patency and no flow limitation. These cases were followed up without performing balloon angioplasty, and all these stenoses regressed to < 10% in 1-year control angiographies. Among four fish mouth cases, two of them showed regression, and one remained the same in angiographic controls. In the other case, fish mouth phenomenon was accompanied with intimal hyperplasia in angiographic examinations.

Additional interventional procedures were required in three patients included in our study. The increase in the size of the aneurysm sac and the persistent progression of the patient's symptoms were determined as the most important criteria for additional treatment decision.

Regarding the six patients presented with subarachnoid hemorrhage preoperatively, one of those patients was treated with flow diverter 30 days after the hemorrhage. The remaining five patients were treated within the first week after the hemorrhage.

The overall stented parent artery occlusion rate was 3% (4/133), and two of these four patients were symptomatic. In our series, permanent morbidity occurred in 4.3% ($n = 7$) of procedures and overall mortality rate was 3.7% ($n = 6$). The

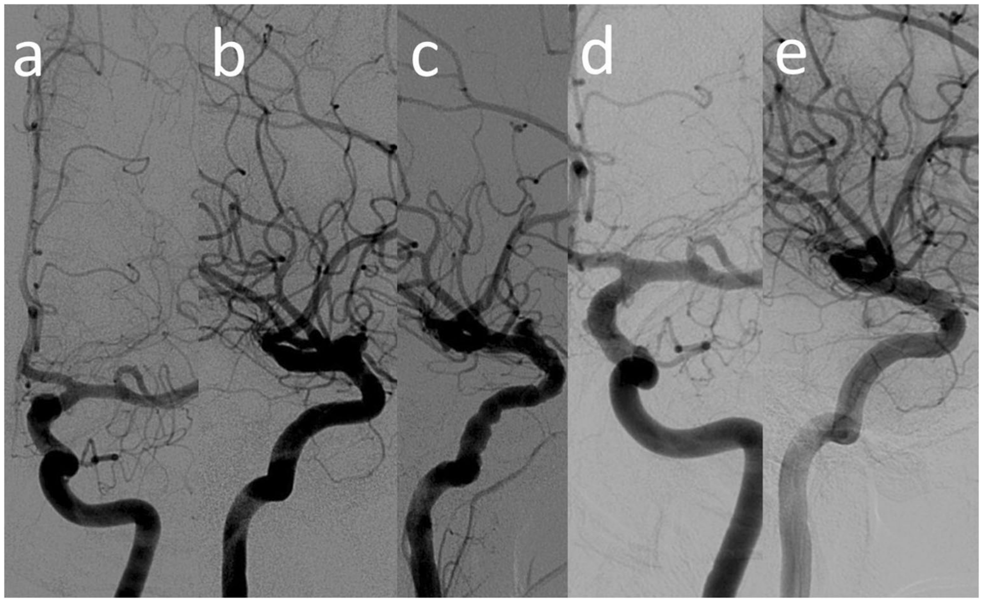

Fig. 2 Digital subtraction angiography (DSA) with anterior-posterior (**a**) and lateral views (**b**) shows a left-sided saccular paraophthalmic aneurysm of internal carotid artery. Following SILK stent implantation, an immediate post-treatment control DSA shows the partial filling (**c**) of the aneurysm. Five-year follow-up DSA with anterior-posterior (**d**) and lateral (**e**) views shows the complete occlusion of the aneurysm with patency of stent lumen

combined major neurologic morbidity and mortality was 8%. One hundred and twenty-five (90.2%) of 133 patients with at least 1-year clinical follow-up had modified Rankin Scale scores ≤ 2.

Table 3 briefly shows the complications and related morbidity-mortality rates.

Discussion

Flow diversion with stents has been designed as a treatment modality for providing progressive occlusion of the aneurysm and long-term hemodynamic healing by reconstructing the parent artery instead of the treatment process by filling in the aneurysm applied in the past for the intracranial aneurysm treatment [16, 22, 26].

In our series, total aneurysm occlusion was achieved in 76.2% at 6 months, 86.7% at 12 months, 93.6% at 3 years, 94.2% at 5 years, and 90.2% during the entire follow-up period (median 927 days) after flow diversion treatment. In the literature, aneurysmal complete occlusion rate was at least 70% at 6 months and progressively increased over time up to 95.2% at fifth year angiographic follow-up [1–4, 11, 14, 16, 17, 21, 22]. Complete occlusion rates detected in the present series is in line with the studies published in the literature and demonstrates the efficacy of flow diverter stents especially in the treatment of complex aneurysms.

Reconstruction of the vascular wall and progressive thrombosis of the aneurysm are the expected outcomes in flow diversion treatment; but this process mainly depends on flow changes, main artery geometry, aneurysm size-shape, and blood coagulation parameters [15]. In the present study, as with all flow diverter stent studies in the literature, the possibility of total occlusion of an aneurysm increases with the time elapsed after treatment, but it is difficult to predict when the total occlusion will occur [5, 9, 11, 14, 16]. Dual

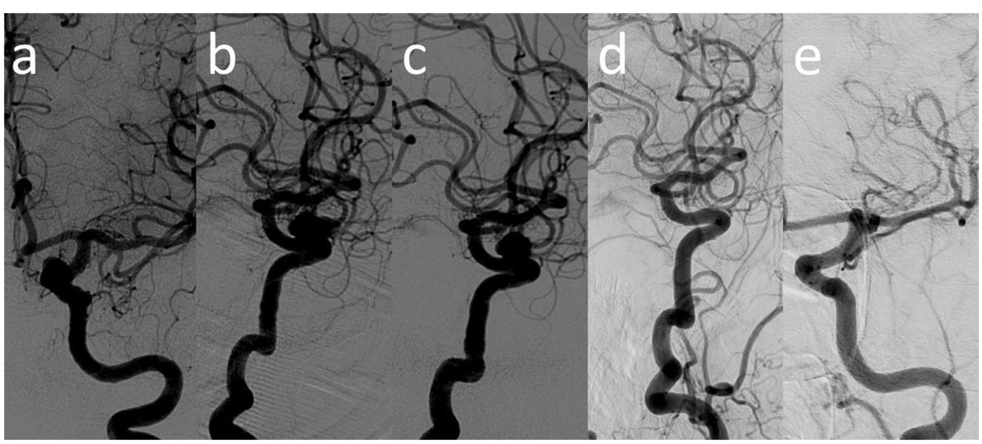

Fig. 3 Digital subtraction angiography (DSA) with anterior-posterior (**a**) and lateral views (**b**) shows a left-sided saccular paraophthalmic aneurysm. Following Pipeline embolization device (PED) implantation, an immediate post-treatment control DSA shows partial filling (**c**) of the aneurysm. Seven-year follow-up DSA with lateral (**d**) and oblique (**e**) views shows the complete occlusion of the aneurysm as well as the reconstruction of the arterial wall and patency of the stent

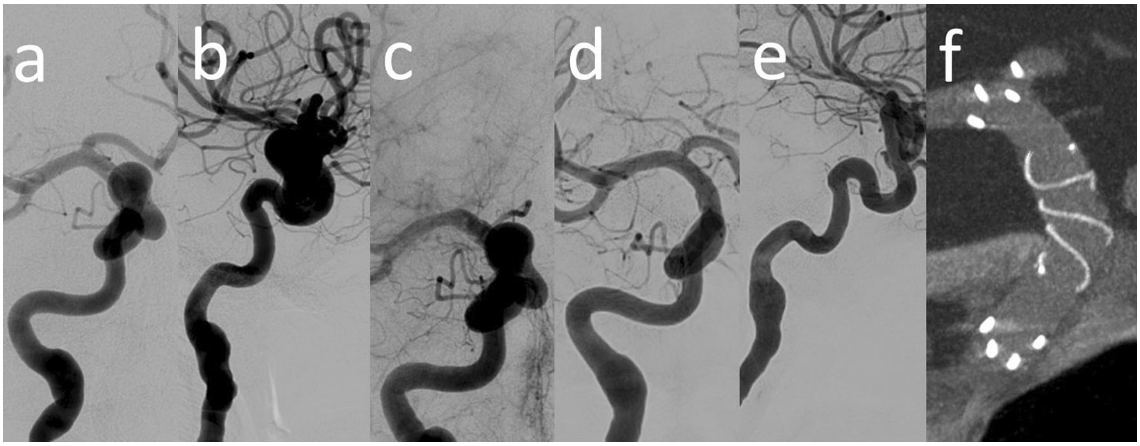

Fig. 4 Digital subtraction angiography (DSA) with anterior-posterior (**a**) and lateral views (**b**) shows a right-sided fusiform paraophthalmic aneurysm. Following FRED stent implantation, an immediate post-treatment control DSA shows complete filling (**c**) of the aneurysm. Seven-year follow-up DSA with anterior-posterior (**d**) and lateral (**e**) views shows the complete occlusion of the aneurysm. Cone-beam computed tomography image (**f**) obtained at the same session shows the well-apposition of the stent to the vessel wall. Note that one of the distal markers is seen in the origin of the anterior cerebral artery, causing no flow disturbance

antithrombotic treatment also contributes to this unpredictability in estimating the exact time of complete aneurysm occlusion.

Multifactorial reasons are thought to play a role in the absence of complete occlusion after flow diverter stent therapy. Among these, effects of dual antiplatelet therapy, variable response to antiplatelet therapy, poor apposition of the stent to the vessel wall, and new hemodynamic environment after flow diverter stent implantation are the most important factors that are responsible for the lack of complete occlusion. According to the occlusion status of the aneurysm and patient's response to antiplatelet therapy, medical treatment can be modified after the evaluation of clinical and laboratory findings. Stent apposition to the vessel wall can also be scanned with flat-panel detector C-arm CT angiography in neuroangiography suite. However, with a retrospective study and in turn limited data, it is more difficult to evaluate the new hemodynamic environment following stent implantation, which may require prospectively designed biophysical studies.

Four cases of transient clinical worsening due to mass effect and six subarachnoid hemorrhages due to aneurysm rupture after stent implantation were observed in our series. Deterioration of mass effect and aneurysm rupture after flow

Fig. 5 Aneurysm occlusion rates

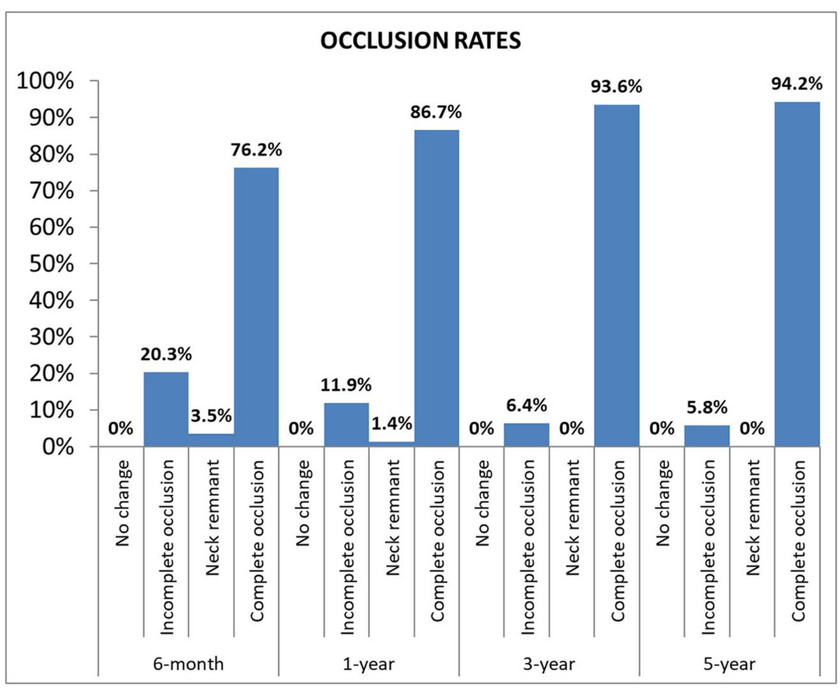

Table 3 Complications, morbidity, and mortality rates

	Values (*n*, %)
Procedural	
Poor apposition to the wall	19 (13%)
Detachment of stent in hub of the microcatheter	2 (1.4%)
Intra-aneurysmal air bubble	1 (0.7%)
Partial collapse in inner stent	1 (0.7%)
Flow diverter stent occlusion	2 (1.4%)
Dissection (ICA petrous segment)	1 (0.7%)
Clinical follow-up period	
Transient worsening of mass effect	4 (3%)
Transient ischemic attack	1 (0.8%)
Fish mouth phenomenon	4 (3%)
Parent artery occlusion	4 (3%)
In-stent stenosis	5 (3.7%)
Ischemic stroke	6 (4.5%)
Delayed hemorrhage	6 (4.5%)
Permanent morbidity	7 (4.3%)
Mortality	6 (3.7%)

ICA internal carotid artery

diverter implantation also suggest that some aspects of the thrombus formation process are uncontrollable and unpredictable. Temporary clinical deterioration due to mass effect was completely resolved in all of these four patients after steroid therapy.

Despite successful implantation of flow diverter stent, delayed hemorrhage may be seen. In these cases, the etiology of the rupture is not clearly understood, but the lytic enzymes and inflammatory mediators secreted during thrombosis process may be responsible of aneurysm wall degeneration. In our series, six subarachnoid hemorrhages due to aneurysm rupture were observed and five of these resulted in mortality. All these patients were symptomatic at presentation and the sizes of the aneurysms were large or giant (18–50 mm). Defined aneurysms were ICA anterior loop aneurysms and ruptured within the first month after treatment.

Kulcsar et al. conducted a study aiming to reveal the characteristics of ruptured aneurysms after flow diversion and showed that symptomatic aneurysms, large or giant aneurysms, and saccular aneurysms with an aspect ratio > 1.6 are more susceptible to rupture [15]. This knowledge has contributed to the current approach of our clinic and since 2014, we have begun to implant flow diverter stent following coiling of the aneurysm sac in symptomatic patients with an aneurysm > 15 mm. Delayed aneurysm rupture following flow diversion is probably a multifactorial problem and pre-clinical studies will be necessary to assess the hemodynamic effects of concomitant coiling and flow diversion treatment.

While recurrence is one of the main concerns in conventional endovascular treatment of intracranial aneurysms, we have not experienced any recurrence after total occlusion or decline in occlusion level. Studies in the literature showed no regression in the grade of occlusion except for a study by Bryne et al. [5].

Changes in-stent morphology such as fish mouthing, which may lead to hemodynamic disturbances in the parent artery flow following flow diversion treatment, may also occur. In our angiographic follow-ups, four fish mouthing phenomena with FRED were detected. The location and temporary nature of this phenomenon suggest that it may be associated with delayed type hypersensitivity to metal constituents of flow diverter stent, and Kocer et al. showed a statistically significant association between fish mouthing and history of contact allergy to imitation jewelry, and a small aneurysm size [13]. Frequent control imaging was recommended in patients with history of contact allergy to detect fish mouthing and its subsequent hemodynamic effects on the flow of parent artery.

In-stent stenosis and parent artery occlusion are also other major concerns about flow diversion treatment. Although heterogeneity exists regarding antiplatelet regimens reported in the literature between different medical centers [7], under dual antithrombotic therapy, these types of complications are seen relatively low and become rarely symptomatic. The overall in-stent stenosis rate and overall stented parent artery occlusion rate in our control angiographies were 3.7% (5/133) and 3% (4/133), respectively. Among these patients only one (1/5) patient with in-stent stenosis and two (2/4) patients with parent artery occlusion were symptomatic. Cases with in-stent stenosis were followed up under dual antiplatelet therapy without performing balloon angioplasty and all stenoses regressed below 10% within 1-year period.

In our series; permanent morbidity rate, overall mortality rate, and combined major neurologic morbidity-mortality rate were found to be 3.7%, 4.3%, and 8%, respectively. A meta-analysis aiming to reveal the outcomes of flow diverters conducted by Brinjikji et al. showed a procedure-related neurologic morbidity rate of 5% and a procedure-related mortality rate of 4% [4].

Limitations

While the flow diverter stents function with the same principle, they show some technical differences in terms of metal content, design, and deployment. These differences may influence rates of occlusion and complication. In our study, 99 SILK stents, 11 PED, and 39 FRED were implanted, and the number of cases was not found sufficient to make statistical discrimination in terms of occlusion rates and complications between different types of flow diverter stents. In short, however, all types of deployed stents have high rates of occlusion and reasonable rates of complications.

We did not present the occlusion rates for the intervals after fifth-year follow-up because our department had no routine angiographic follow-up after 5 years except tenth year unless the aneurysm occlusion status is incomplete; the number of patients decreased in the subsequent follow-up periods (for instance, only 21 patients after sixth year). Another reason for this decrease was the patients' incompliance and reluctance to long-term follow-up. Since the imbalanced distribution due to limited number of patients following sixth-year follow-up could provide misleading results, these data were not statistically analyzed. Nonetheless, for the future, our clinic also plans to update our long-term follow-up study by reporting the occlusion rates after tenth-year angiographic control, to reflect aneurysm occlusion process in a broader period with more detail.

Conclusion

Flow diverters are relatively new and effective tools in the management of complex aneurysms with reasonable rates of morbidity and mortality. Radiological follow-up results of these stents showed high aneurysm occlusion rate and durable treatment with high parent artery patency.

Compliance with ethical standards

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest NK and CI have consultancy and proctoring agreement with Microvention, Inc.

Study-cohort overlap Some of the patients' short- and mid-term results were reported in authors' other previous studies. But the focus of this study is the long-term results.

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