Flow Diverter Treatment for Non-Ruptured Carotid Aneurysms: Efficacy and Safety

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Purpose: Internal carotid artery (ICA) aneurysm treatment with a flow diverter (FD) has shown an adequate efficacy and safety profile, presenting high complete occlusion or near occlusion rates with low complications during follow-up. The purpose of this study was to evaluate the efficacy and safety of FD treatment in non-ruptured internal carotid aneurysms.

Materials and Methods: This is a retrospective, single-center, observational study evaluating patients diagnosed with unruptured ICA aneurysms treated with an FD between January 1, 2014, and January 1, 2020. We analyzed an anonymized database. The primary effectiveness endpoint was complete occlusion (O'Kelly–Marotta D, OKM-D) of the target aneurysm through 1-year follow-up. The safety endpoint was the evaluation of modified Rankin Scale (mRS) 90 days after treatment, considering a favorable outcome an mRS 0-2.

Results: A total of 106 patients were treated with an FD, 91.5% were women; the mean follow-up was 427.2±144.8 days. Technical success was achieved in 105 cases (99.1%). All patients included had 1-year follow-up digital subtraction angiography control; 78 patients (73.6%) completed the primary efficacy endpoint by achieving total occlusion (OKM-D). Giant aneurysms had a higher risk of not achieving complete occlusion (risk ratio, 3.07; 95% confidence interval, 1.70 - 5.54]). The safety endpoint of mRS 0-2 at 90 days was accomplished in 103 patients (97.2%).

Conclusion: Treatment of unruptured ICA aneurysms with an FD showed high 1-year total occlusion results, with very low morbidity and mortality complications.

Key Words: Endovascular procedures; Aneurysm; Stents; Treatment outcome; Safety; Complications

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INTRODUCTION

The presence of brain unruptured aneurysms is estimated to be between 2% and 5%,[1] and most of them have a silent clinical course,[2,3] but their rupture can trigger a subarachnoid hemorrhage (SAH) of variable severity.[4,5] The mortality of SAH is high, approximately 35%, with morbidity at around 30%.[6] One-third of patients who survive remain with irreversible neurological sequelae and without achieving functional independence, which is ideally why this should be treated prior to rupture.[7-9]

Endovascular management has become the standard treatment for cerebral aneurysms. In recent years, the use of this treatment has increased from 17 to 58% and continues to rise.[6,10] The use of flow diverters (FDs) was initially considered for complex unruptured aneurysms, which may not be amenable to conventional coiling.[3] FD stenting, despite being an excellent alternative, could have ischemic and hemorrhagic complications and variable occlusion rates related to the aneurysms and patient characteristics.[11,12] Other studies have examined the efficacy and safety of FD stenting for carotid aneurysms with variable results.[13,14] Most recently, the Prospective study on embolization of intracranial aneurysms with pipeline embolization device (PREMIER) study[15] focused on small and medium intracranial aneurysms with a 76.6% occlusion rate at 1 year.

This retrospective single-center study aims to evaluate the efficacy and safety in patients with non-ruptured carotid aneurysms treated with FD.

MATERIALS AND METHODS

Study Design, Enrollment, and Patient Selection

This is a retrospective, single-center, observational study evaluating patients diagnosed with unruptured intracranial internal carotid artery (ICA) aneurysms treated with an FD stent between January 1, 2014, and January 1, 2020, at the Fundación Oftalmológica de Santander–Clínica Ardila Lülle. We analyzed and anonymized patient information that may identify a patient from clinical records, medical consultations, and follow-up imaging records of the patients enrolled. Patients over 18 years of age with a diagnosis of unruptured small (<5 mm), medium (5–10 mm), large (10–25 mm), or giant (>25 mm) aneurysms of the intracranial internal carotid segment treated with FDs in that period were included. In addition, 1-year digital subtraction angiography (DSA) results were mandatory to assess the occlusion rate. Incomplete data in the database, patients with no follow-up, and a history of aneurysm rupture less than 30 days before treatment were excluded.

Baseline Assessment

Before placement of the FD, patients underwent a baseline clinical assessment using the modified Rankin Scale (mRS). Medical history, pre-existing conditions, and reason for treatment were documented. Baseline imaging consisted of computed tomography angiography, magnetic resonance angiography (MRA), or DSA with 3D reconstruction, taken within the prior treatment. Twenty-one patients selected for FD treatment had different types of previous interventions, including endovascular or clipping surgery.

Dual Antiplatelet Strategy

All patients received dual antiplatelet treatment 7 days before treatment using aspirin (100 mg/day for 7 days) and clopidogrel (75 mg/day for 7 days) before surgery. Most of the patients were tested for antiplatelet drug response using VerifyNow® (Accumetrics) the day before FD implantation. P2Y12 reaction units (PRUs) were required below 200. Patients with a PRU above 200 were changed to a ticagrelor and aspirin regime (Ticagrelor 180 mg loading dose, and continue 90 mg/12 h). After the procedure, patients continued dual antiplatelet therapy with aspirin-clopidogrel or aspirin-ticagrelor for at least 6 months. After 6 months, the clopidogrel or ticagrelor was removed, and patients continued with aspirin for at least 1 year.

Study Devices and Procedure

All procedures were performed under general anesthesia by using a standard transfemoral approach. Intravenous heparin was administered at 50–100 U/kg to achieve an activated clotting time >200 s. Different types of FDs were used, selected by specialist decision. Each procedure was performed by 2 neurointerventional radiologists with experience of at least 20 FD implantations.

Patients' Follow-up

Patients underwent neurological assessment at 8 days with external consultation of an interventional radiologist and at 6 months post-procedure with MRA. Follow-up DSA was mandatory at 1 year, and results were evaluated for the degree of

aneurysm occlusion according to the O'Kelly–Marotta scale (OKMs),[16] the presence and degree of parent vessel stenosis according to the methods of Samuels et al.,[17] and the occurrence of implant migration if seen.

Primary Endpoints

The primary effectiveness endpoint was complete occlusion (OKMs) of the target aneurysm through a 1-year follow-up. The primary safety endpoint was the evaluation of mRS 90 days after treatment. A favorable safety outcome was defined as an mRS 0-2 after treatment.

Secondary Endpoints

Secondary endpoints included immediate perioperative complications (thromboembolic, hemorrhagic, device-related, and vascular access-related). Late complications at 12 months (intimal hyperplasia, stent shortening or migration, visual disturbances, neurovascular syndromes, and late rupture) were described in the population studied. Also, the antiplatelet pharmacological strategy used was detailed along with its relationship to possible complications according to the use or not of VerifyNow®. The technical success of the procedure in the adequate release of the device was quantified.

Statistical Analysis

Information extraction was done in Excel® (Microsoft) and the statistical analysis in the STATA® software (StataCorp). Qualitative variables are described with absolute and relative frequency and their respective 95% confidence intervals. Quantitative variables are calculated as measures of central tendency, mean, and standard deviation. The technical success rate of the procedure in the adequate release of the device is estimated. Association measures are carried out to establish a relationship between the variables of interest. Bivariate analysis of the variables of interest is carried out, making comparisons using the corresponding statistical test according to the distribution and nature of the variables (chi-square). With the chi-squared test, the association between the occlusion rates after treatment at 12 months will be evaluated using the OKMs.[16] Fisher's exact test for qualitative variables is used. Relative risk was calculated in variables in which significant differences were found. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics

A total of 109 patients with unruptured intracranial ICA aneurysms were treated in the selected period. Three of these patients were excluded; 2 of them had incomplete information with no year follow-up DSA, and the other 1 was treated in the acute stage after aneurysmal SAH. In total, 106 patients met the inclusion criteria; 97 (91.5%) were women. The mean age was 61.0±14.1. The mean follow-up was 427.2±144.8 days. Thirteen patients (12.3%) had a family history of brain aneurysms, 63 (59.4%) had multiple brain aneurysms, and 18 (17.0%) had a personal history of previous SAH. Eighty-

Table 1. Patient and aneurysm characteristics (n=106)

Characteristic	Data
Demographics	
Age (y)	61.0±14.1
Women	97 (91.5)
Follow-up (d)	427.2±144.8
Medical history	
Hypertension	49 (46.2)
Smoking history	11 (10.4)
SAH history	18 (17.0)
Familiar history	13 (12.3)
Multiple aneurysms	63 (59.4)
Aneurysm size	
Small (<5 mm)	38 (35.9)
Medium (5-10 mm)	49 (46.2)
Large (10-25 mm)	12 (11.3)
Giant (>25 mm)	7 (6.6)
Aneurysm location in ICA	
PCom segment	28 (26.4)
Ophthalmic segment	61 (57.6)
Cavernous segment	10 (9.4)
Choroidal segment	7 (6.6)
Aneurysm type	
Saccular	103 (97.2)
Fusiform	1 (0.9)
Blood blister like	1 (0.9)
Dissecting	1 (0.9)

Values are presented as mean±standard deviation or number (%).
SAH, subarachnoid hemorrhage; ICA, internal carotid artery; PCom, posterior communicating artery.

five patients (80.2%) were tested the day before treatment to the response to P2Y12 receptor antagonists, and 12 (11.3%) required a change of antiplatelet therapy to aspirin and ticagrelor. The patients not tested for platelet function were due to the absence of this technology at the time of the intervention (Table 1).

Among the 106 cases included, 61 (57.6%) were in the ophthalmic segment, 28 (26.4%) were in the posterior communicating segment, 10 (9.4%) in the cavernous segment, and 7 (6.6%) in the choroidal segment. Thirty-eight were small aneurysms <5 mm (35.9%), 49 were medium size 5–10 mm (46.2%), 12 were large 10–25 mm (11.3%), and 7 aneurysms were giant >25 mm (6.6%). In addition, 103 aneurysms were saccular (97.2%), 1 was fusiform, 1 was blood-blister, and 1 was a dissecting aneurysm, each representing 0.9%. Twenty-one patients (19.8%) had previous treatment; 3 (2.8%) were previously clipped, 12 (11.3%) had conventional coiling, 1 (0.9%) had coils and an FD stent, 2 (1.9%) had coils and a non-FD stent, and 3 (2.8%) a previous FD stent without coiling. All the above were selected for new treatment. During the new intervention, physicians decided the need for additional coiling; 30 aneurysms (28.3%) were also treated with coils. Four giant aneurysms (3.8%), 10 large (9.4%), 10 medium (9.4%), and 6 small aneurysms (5.7%) were considered for additional coiling. Twenty-one cases (19.8%) required balloon angioplasty for optimal FD wall apposition by the decision of the treating physician.

Technical success was achieved in 99.1%, and only 1 case of insufficient wall apposition was seen in low-contrast intraprocedural DSA imaging. Different types of FDs were used: 83 (78.3%) were Pipeline (Medtronic), 16 (15.1%) Silk (Balt Extrusion), 3 (2.8%) were P-64 (Phenox GmbHand 4 (3.8%) were Fred (MicroVention) (Table 1, 2).

Primary Endpoints
All patients included had 1-year follow-up DSA control. Seventy-eight of 106 cases (73.6%) completed the primary efficacy endpoint by achieving total occlusion (OKM-D). Twenty-eight of 106 cases (26.4%) did not reach this primary endpoint: 8 cases (7.6%) OKM-A, 4 cases (3.8%) OKM-B, and 16 cases (15.1%) OKM-C. Association was assessed between 1-year occlusion and each aneurysm group size, with no statistical difference found between them (P=0.216). Since no statistical difference was found in the occlusion endpoint between small, medium, and large aneurysms (P=0.705), the occlusion variable was dichotomized between complete

occlusion (OKM-D) and other grades of occlusion (OKM-A, B, C), finding statistical differences when associated to the aneurysm group size (P=0.036). Giant aneurysms showed a statistical difference in achieving complete occlusion (P=0.005), with 3 times the risk of not achieving complete occlusion at 1-year follow-up (risk ratio [RR], 3.07; 95% confidence interval [CI], 1.70–5.54) when compared to the other 3 group sizes (Table 3).

Table 2. Periprocedural details (n=106)

Characteristic	Data
Technical success	105 (99.1)
Previous treatment	21 (19.8)
Clip	3 (2.8)
Conventional coiling	12 (11.3)
Coiling and FD	1 (0.9)
Coiling and non-FD stent	2 (1.9)
FD alone	3 (2.8)
Balloon angioplasty	21 (19.8)
Additional coiling	30 (28.3)
Small (<5 mm)	6 (5.7)
Medium (5–10 mm)	10 (9.4)
Large (10–25 mm)	10 (9.4)
Giant (>25 mm)	4 (3.8)
Platelet function evaluation	85 (80.2)
Dual antiplatelet strategy	
Aspirin+clopidogrel	94 (88.7)
Aspirin+ticagrelor	12 (11.3)
Type of flow diverter	
Pipeline	83 (78.3)
Silk	16 (15.1)
P64	3 (2.8)
Fred	4 (3.8)

Values are presented as number (%).
FD, flow diverter.

Table 3. Grades of occlusion using OKMs

Aneurysm size	Aneurysm occlusion		P-value
	OKM-D	OKM-A, B, C	
Small (n=38)	31 (81.6)	7 (18.4)	0.705
Medium (n=49)	36 (73.5)	13 (26.5)	
Large (n=12)	9 (75.0)	3 (25.0)	
Giant (n=7)	2 (28.6)	5 (71.4)	
Total (n=106)	78 (73.6)	28 (26.4)	0.036

The safety endpoint of mRS 0-2 at 90 days was completed by 103 patients (97.2%). Three patients (2.8%) had mRS>2; 1 patient presented aneurysm rupture (0.9%) during treatment with mRS 0-2 at 90 days; and 1 patient (0.9%) presented 6 weeks later with minor ischemic stroke (National Institutes of Health Stroke Scale 4) with an adequate response to thrombolysis after covering the anterior choroidal artery (previous PRU 181) with mRS 0-2 at 90 days. One patient died (0.94%) 4 weeks after treatment due to severe intraparenchymal cerebral hemorrhage, after anticoagulation adjustments for atrial fibrillation (AF). This patient received aspirin and ticagrelor after finding a PRU of 240 before treatment; rivaroxaban was added for AF 1 month after treatment.

Secondary Endpoints

During and after treatment, early complications (1 week) were documented in 4 patients with 6 aneurysms (5.7%). The first patient was treated with FD stents in 2 aneurysms of the left middle cerebral artery in the M1 segment and 1 aneurysm in the posterior communicating segment. After stent placement, angiographic control was performed showing stenosis in 2 segments of the stent. Therefore, balloon angioplasty was performed. In the following angiographic control, extravasation of the contrast medium secondary to rupture of the left middle cerebral artery was evidenced, so Tirofiban infusion was suspended and heparin was reversed with protamine. It was decided to perform occlusion with coils with no filling in the left middle cerebral artery. The second patient with an aneurysm in the right middle cerebral artery was embolized with coils. Angiographic control showed rupture of the aneurysm without hemodynamic manifestations; stent placement was used to compact the coil and control the hemorrhage. Subsequently, angiographic control was performed with correct bleeding control, for which the solitary stent was removed. Subsequently, the FD was released from the bifurcation of the right internal cerebral artery to the ophthalmic segment. Angiographic controls revealed 100% occlusion of the aneurysm and patency of the distal arteries. The third patient was treated in 2016 for 2 aneurysms at the level of the ophthalmic segment of the right ICA with a SILK stent completely covering the neck of both aneurysms. In annual control, there was a persistent filling of the aneurysms with retention of the contrast medium until the late venous phase with OKM A; therefore in 2017, Pipeline stent embolization was performed with the stent technique for an OKM B result. One week after the treatment, she presented with

intraparenchymal hemorrhage due to an overdose of clopidogrel, mistakenly doubling the dose. The fourth patient had 3 aneurysms located in the cavernous, ophthalmic, and posterior communicating segment of the right ICA, the last one with signs of bleeding, which were embolized with coils, evidencing complete occlusion. Subsequently, chemical angioplasty of the right middle cerebral artery was performed for 5 minutes with good angiography response to cerebral vasospasm. After 7 days, it was decided to implant a pipeline stent covering the neck of the 3 aneurysms. In angiographic control, there is the retention of the contrast medium in the aneurysm of the cavernous and communicating segment.

Late complications (12 months) were also measured: intimal hyperplasia <50%, FD shortening, or migration, and visual disturbances were seen in 4 cases each (3.8%). One case (0.9%) of ischemic stroke was registered as mentioned previously, and no cases of late ruptured. No statistical difference was found between the ICA segment affected (P=0.956), the type of FD used (P=0.130), the dual antiplatelet strategy (P=0.906), or the 90 days mRS (P=0.783) when associated with the occlusion rate assessed with the OKMs. No association was found between patients tested for platelet function and complications.

DISCUSSION

This study enrolled all sizes of ICA aneurysms, and different types of FD were used for treatment proposes. After 1-year angiographic follow-up, 73.6% of the patients showed complete occlusion (OKM-D), reaching the primary efficacy endpoint. On the other hand, 26.42% had incomplete occlusion (OKM-A, B, C). When individually assessing the 1-year angiographic results, no statistical differences were found between small, medium, and large aneurysms. They had similar efficacy results (81.5% *vs.* 73.4% *vs.* 75.0%, respectively; P=0.705), something not seen in giant aneurysms (28.6%, P=0.036). When comparing giant aneurysms to the other aneurysm sizes grouped, a statistical difference was found regarding total occlusion (76.8% *vs.* 28.6%; P=0.005), with 3 times the risk of not achieving total occlusion at 1-year follow-up (RR, 3.07; 95% CI, 1.70–5.54; Table 3). Late rupture cases were not documented in this study.

Other authors have studied occlusion outcomes in follow-up imaging, with similar findings compared to our results. The Pipeline for uncoilable or failed aneurysms (PUFS)

study[13] documented complete occlusion of 73.6% at 180 days and 86.6% at 1 year after treatment for ICA aneurysms >10 mm. However, nearly 80% of all aneurysms in their study were small or medium size (≤12 mm).[14] Two meta-analyses by Brinjikji et al.[18] and Briganti et al.[19] reported a complete occlusion rate of 76% and 81.5%, respectively. Both studied intracranial aneurysms including different territories; nevertheless, ICA aneurysms were prevalent in up to 90% of the included cases. Recently, the PREMIER study[15] also reported 1-year occlusion results of 76.6%, controlling 97.9% of their sample with DSA control.

Safety outcomes have also been a concern for other authors. The InterPED study[14] was able to enroll a larger sample (793 patients) to evaluate morbidity and mortality rates and included all intracranial territories. The neurologic morbidity and mortality for unruptured ICA aneurysms >10 mm group was 9.2% and the ICA <10 mm group was 4.1% higher than the present study. The PREMIER study reported 2.1% of morbidity and mortality, and PUFS 5.6% of its patients had a major ipsilateral stroke and neurologic death by day 180.[13,15]

In the first week after treatment, 6 of 106 complications (5.7%) were listed: 2 patients had SAH due to aneurysm rupture during treatment, 2 had parenchymal hemorrhages with previously normal PRU, and 2 had femoral access hematomas that didn't require further interventions or threaten the patient's life. Of all patients who received dual antiplatelet therapy, 88.7% received aspirin and clopidogrel or 11.32% received aspirin and ticagrelor. The response to P2Y12 receptor antagonists was tested in most of our patients (80.2%). The PREMIER study considered this testing as a mandatory variable for patient inclusion with values of 60–200 PRU.[15] No statistical differences were found between the use of VerifyNow®, the anti-aggregation therapy, or the type of FD used with any of the primary endpoints or complications.

Adequate follow-up was mandatory to control the primary endpoints of interest. The mean follow-up was 427.2±144.8 days. Also, all patients included had control DSA and clinical consultations to evaluate results and mRS, which is a strength of this study.

The principal limitations of this study are that this is a single-center, retrospective nonrandomized study. Some patients were treated additionally with coiling along with an FD at the operators' discretion. However, this may have introduced some bias in the primary outcomes.

CONCLUSION

This study suggests that the treatment of unruptured ICA aneurysms with an FD is a treatment that demonstrates high efficacy and safety as shown by the complete occlusion results at 1-year along with favorable clinical outcome (mRS 0-2). Patients with giant aneurysms were more likely to fail in achieving complete angiographic occlusion.

Ethics Statement
The registry satisfies all requirements mandated by Colombian law on the protection of personal data. The ethics committee of Fundación Oftalmológica de Santander–Clínica Ardila Lülle approved the study (no. 05420/2021). We analyzed an anonymized database containing information from clinical records, medical consultations, and follow-up imaging results of the patients enrolled after the approval of the ethics committee. Before any intervention, all patients provided signed informed consent.

Conflicts of Interest
The authors have no conflicts to disclose.

Author Contributions
Concept and design: OL-C. Analysis and interpretation: OL-C, DAR-R, and DDV. Data collection: ABV-B, DDV, and AFO-G. Writing the article: ABV-B and DAR-R. Critical revision of the article: AFO-G, CAF-P, OV-P, MG, and DM. Final approval of the article: AFO-G, CAF-P, OV-P, MG, and DM. Statistical analysis: SS-G and AR-G. Overall responsibility: DM.

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