Original Paper

Stenting and Angioplasty of Small Cerebral Arteries in Symptomatic Intracranial Atherosclerotic Disease

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Key Words

Intracranial atherosclerotic disease · Small intracranial arteries · Angioplasty · Stenting · Wingspan

Abstract

Background: Intracranial atherosclerotic disease (ICAD) is a common cause of stroke with a poor natural history despite medical therapy. Few studies have investigated endovascular therapies for the treatment of symptomatic ICAD in distal intracranial arteries. Here, we present the feasibility and safety of balloon angioplasty with and without stenting in patients with medically refractory small-artery symptomatic ICAD. **Methods:** Personal logs were reviewed to identify patients who were treated for small-artery ICAD (stenosis >50%) using angioplasty and/or stenting. Small cerebral arteries were defined by a diameter of ≤2 mm or any branch distal to a large intracranial vessel (i.e. distal to the internal carotid artery, M1, A1, or vertebrobasilar trunk). Patient characteristics, clinical manifestations, treatment, hospital course, and follow-up data were collected and analyzed. **Results:** Ten patients (12 arteries) were treated with either primary balloon angioplasty (58.3%) or angioplasty with stenting (41.6%) with a 100% technical success rate. Mean pretreatment stenosis was 79.9%, while mean posttreatment stenosis was 19.0%. There were no major periprocedural complications, including symptomatic intracranial hemorrhage or mortality; 3 cases were complicated by groin hematoma. Patients were followed for a mean total of 18.6 months with only 1 symptomatic restenosis which was retreated successfully. All patients had good functional outcome with a modified Rankin Scale of either 0 (80%) or 1 (20%) on follow-up. **Conclusion:** In our case series, treatment of symptomatic small-artery ICAD with angioplasty and/or stenting was safe and effective. These interventions should be considered as an alternative treatment for ICAD patients refractory to medical therapy.

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Introduction

Intracranial atherosclerotic disease (ICAD), a common cause of acute ischemic stroke, accounts for 8–10% of cases in the United States and for as many as 33% of cases in the Asian population [1, 2]. Unfortunately, ICAD has a high stroke recurrence rate that correlates with the severity of stenosis and, during the first year, can be as high as 18% for patients with $\geq 70\%$ stenosis [3, 4]. The natural history of ICAD is not well understood; however, it has been associated with age, hypertension, and diabetes mellitus [5]. Primary treatment of ICAD involves antiplatelet therapy, statins, and modification of cardiovascular risk factors such as hypertension, diabetes, and smoking. Unfortunately, despite medical treatment, many patients remain symptomatic. In the past, surgical approaches such as extracranial-intracranial arterial bypass have failed to show improved efficacy over medical treatment [6]; however, during the past decade, percutaneous transluminal angioplasty with stenting (PTAS) has become a prevalent rescue therapy in these patients. Currently, the Wingspan Stent System with Gateway™ balloon is the only Food and Drug Administration-approved PTAS device for ICAD patients refractory to medical therapy and stenosis of $\geq 50\%$, and various studies have investigated its efficacy and safety since its introduction in 2005 [7–11]. The SAMMPRIS trial (Stenting vs. Aggressive Medical Therapy for Intracranial Arterial Stenosis) remains to be the only randomized controlled trial, reporting that aggressive medical management is superior to PTAS in large-artery ICAD treatment (artery diameter of 2–4.5 mm) [12].

Interestingly, there are very few studies looking at the feasibility of primary angioplasty or PTAS in small intracranial artery atherosclerosis. In this study, we will present our experience with primary angioplasty or PTAS of small-artery ICAD.

Methods

Following institutional review board approval, we retrospectively reviewed all angioplasty and PTAS cases performed by our group at the Medical College of Wisconsin from January 2005 through July 2009. Inclusion criteria included: (1) medically refractory and symptomatic ICAD patients with $\geq 50\%$ stenosis in the same vascular territory using computed tomography angiography (CTA) or digital subtraction angiography (DSA) and (2) presence of small intracranial artery involvement (defined as arteries with a diameter of ≤ 2 mm or any distal branch of large intracranial arteries, i.e. distal to the M1, A1, or vertebrobasilar trunk). Exclusion criteria included: (1) non-atherosclerotic stenosis, cardioembolic source, antiplatelet contraindication, poor functional baseline [modified Rankin Scale (mRS) ≥ 2] and (2) concomitant disease with survival < 2 years. Of the 169 intracranial angioplasty and stenting procedures identified, 10 eligible patients (12 interventions) were selected for which demographic, procedural, radiographic, and clinical follow-up data were collected for at least 2 months. Functional outcome was measured using the mRS from patients' last known clinic visit with good outcome defined as mRS ≤ 2 , and intracranial stenosis was measured as previously described [13]. All procedures were performed under general anesthesia, and our protocol included preprocedural heparin (2,000–6,000 units) and dual antiplatelet therapy with clopidogrel (75 mg) and aspirin (325 mg) at least 3 days before and 3 months after procedure, when possible. Angioplasty was done using the Gateway balloon in all cases except 2 (Maverick™ balloon), and PTAS was performed using the Wingspan Stent System. Following the procedure, patients were monitored for 24 h in the neurointensive care unit.

Results

Patient Characteristics

The study included 10 patients (3 men and 7 women) with symptomatic small-artery ICAD and a mean age of 66.6 years (range 38–85 years). The mean time from initial symptom to interventional procedure was 4.8 months (ranging from 3 days to 6 months). There were

Table 1. Summary of characteristics, stenosis, treatment, and follow-up in patients with small-artery ICAD

Case No.	Age, years/sex	Comorbidity	Site	Stenosis, %		Time of onset to Tx	Balloon, mm	Stent	Complication	Last follow-up		Aspirin and plavix duration
				pre	post					imaging	clinical	
1	64/M	HTN, HLD	P2	80	10	3 days	Gateway 2 × 9	WS 3.5 × 15	none	11 months, CTA, patent with intimal hyperplasia	11 months, mRS 0	3 days, then plavix and warfarin
2.1	85/F	HTN, TIA	A3	99	10	1 month	Gateway 1.5 × 9	none	none	2 months, DSA, 95% restenosis	2 months, mRS 1 (intermittent Sx)	indefinite
2.2	85/F	HTN, TIA	A3	99	10	2 months	Gateway 2.5 × 15	WS 3.5 × 9	none	1 month, CTA, patent	12 months, mRS 0	indefinite
3	65/F	HTN, HLD, CAD, stroke	P2	67	14	3 months	Gateway 2.5 × 15	WS 3 × 15	none	68 months, CTA, patent	68 months, mRS 0	indefinite
4	56/M	HTN, HLD, CAD, TIA	A3	55	20	1 month	Gateway 2 × 9	none	none	1 month, CTA, patent	33 months, mRS 1	3 days, then aspirin only
5.1	38/F	HTN, DM, HLD, CAD, stroke	P2	95	20	2 weeks	Gateway 2 × 15	none	groin hematoma	14 months, CTA, <50% restenosis	14 months, mRS 0	indefinite
5.2	38/F	HTN, DM, HLD, CAD, stroke	P2	55	20	2 weeks	Gateway 15 × 15	none	groin hematoma	14 months, CTA, <50% restenosis	14 months, mRS 0	indefinite
6	76/F	HTN, DM, HLD, TIA	A2	80	20	4 months	Maverick 1.5 × 9	none	none	none	2 months, mRS 0	2 months, then plavix daily
7	83/F	DM	M2	75	20	3 weeks	Gateway 2 × 9	WS 3.5 × 15	none	29 months, CTA, patent with intimal hyperplasia	29 months, mRS 0	indefinite
8	75/F	HTN, HLD, TIA	PICA	75	20	6 months	Gateway 2 × 9	none	groin hematoma	5 months, CTA, patent	5 months, mRS 0	3 months, then aspirin daily
9	75/M	HLD	M2/M3	99	30	3 days	Maverick 1.5 × 9	none	none	21 months, CTA, <50% restenosis	22 months, mRS 0	indefinite
10	49/M	HTN, HLD, TIA	P2	80	35	1 month	Gateway 1.5 × 15	WS 3 × 15	none	11 months, CTA, 45% restenosis	11 months, mRS 0	indefinite

A = Anterior cerebral artery; CAD = coronary artery disease; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension; M = middle cerebral artery; P = posterior cerebral artery; PICA = posterior inferior cerebellar artery; Sx = symptoms; TIA = transient ischemic attack; Tx = treatment; WS = Wingspan.

12 lesions in 10 patients that were equally distributed in both anterior and posterior circulations (table 1). Both primary balloon angioplasty and PTAS with Wingspan were technically successful in all patients. The mean preprocedure stenosis was 79.9% (range 55–99%) with a mean residual stenosis of 19.0% (range 10–35%). Primary balloon angioplasty was performed using either Gateway (71.4%, 5 of 7 patients) or Maverick balloon (28.6%, 2 of 7 patients), while Wingspan was used in all stenting procedures.

Hospital Course and Complications

The mean hospital stay for all patients was 6.8 days. There were no significant periprocedural complications, such as symptomatic intracranial hemorrhage or mortality; however, 3 patients developed groin hematomas.

Follow-Up

The initial clinical follow-up was done after a mean of 50.4 days and continued for a mean total of 18.6 months. Only 1 patient (No. 2) who underwent primary angioplasty returned with symptomatic restenosis necessitating retreatment with PTAS. The duration of dual antiplatelet treatment was indefinite for 6 patients, 2–3 months for 2 patients, and indefinite monotherapy for the other 2 patients due to either allergy or intolerance. Good functional outcome (mRS ≤2) was seen in all patients at the time of their last follow-up.

Example Case 1

A 64-year-old Caucasian male with a history of dyslipidemia, pulmonary embolism, and transient ischemic attack presented to the emergency department with acute visual distur-

Fig. 1. A 64-year-old male presenting with visual disturbances and disequilibrium was found to have a $\geq 80\%$ stenosis of the right P2 on DSA (**a**; arrow). The patient's symptoms resolved after PTAS with minimal ($\sim 10\%$) residual stenosis (**b**; arrow). After 11 months, follow-up CTA shows mild intimal hyperplasia on sagittal and coronal views (**c** and **d**, respectively; arrows).

bance, headache, and disequilibrium. Initial CTA and subsequent DSA confirmed an 80% stenosis within the right proximal P2 segment of the posterior cerebral artery (PCA) (fig. 1a). Since the patient was previously on maximal medical therapy, he successfully underwent angioplasty of the stenotic lesion via the right internal carotid posterior communicating arteries (Gateway balloon; 2×9 mm) with an inflation pressure reaching up to 10 atmospheres. The balloon was then exchanged for a Wingspan stent (3.5×15 mm) with a residual stenosis of 10% (fig. 1b). The procedure was tolerated without any periprocedural complications and follow-up CTA of the head illustrated mild intimal hyperplasia after 11 months (fig. 1c, d).

Fig. 2. An 85-year-old female presenting with left lower extremity shaking was found to have >95% stenosis of the right A3 portion of the anterior cerebral artery (**a**; arrow). Despite aggressive medical management, the patient continued to have recurrent symptoms and underwent successful primary balloon angioplasty (**b**; arrow). However, the patient returned with symptomatic restenosis (>95%) after 1 month (**c**; arrow) and subsequently underwent PTAS through deployment of two Wingspan stents in a telescoping fashion into the right A3 lesion. Final angiography revealed minimal residual stenosis (**d**; arrow).

Example Case 2

An 85-year-old Caucasian female with a history of hypertension and transient ischemic attack presented with involuntary limb shaking and twitching of the left lower extremity. After excluding possible radiculopathy and seizure, magnetic resonance imaging (MRI) and MR angiography of the brain showed a right corpus callosum infarction and significant narrowing of the right anterior cerebral artery. The patient continued to have recurrent symptoms despite maximal medical therapy with repeat DSA after 6 months, showing right A3 stenosis (>95%) 10 mm in length (fig. 2a). The patient was then treated with primary balloon angioplasty (Gateway balloon; 1.5 × 15 mm) as shown in figure 2b. However, after 1 month, the patient was readmitted for similar symptoms and was found to now have >95%

Fig. 3. A 65-year-old female with right lower extremity weakness was found to have small left thalamic and posterior internal capsule infarcts along with 67% stenosis in the left P2 segment of the PCA as shown in lateral and frontal views of selective left vertebral DSA (**a** and **b**, respectively; arrows). The patient underwent successful PTAS with the Wingspan Stent System with resultant 14% residual stenosis as seen on frontal and lateral views (**c** and **d**, respectively; arrows).

restenosis (fig. 2c). She underwent PTAS of the right A3 vessel using the Wingspan Stent System with only a 10% residual stenosis as seen in figure 2d. No periprocedural complications occurred and the patient demonstrated a mRS of 0 at 12 months.

Example Case 3

A 65-year-old Caucasian female with a past medical history of hypertension, diabetes, and hyperlipidemia was admitted for right lower extremity weakness and was found to have left thalamic and posterior internal capsule strokes along with a high-grade stenosis of the left P2 segment (67%, 11.6 mm in length) of the PCA (fig. 3a, b). Prior to the stroke, the patient was on maximal medical therapy (including dual antiplatelets). The patient underwent balloon angioplasty (Gateway balloon; 2.5 × 15 mm) with an inflation pressure up to 8 atmospheres, followed by successful deployment of Wingspan stent (3 × 15 mm) across the lesion and minimal residual stenosis (fig. 3c, d). During her 5-year follow-up, she continued to have a widely patent stent on CTA and a good functional outcome (mRS = 0).

Table 2. Comparison of current data on endovascular treatment of small-artery ICAD [14–17]

Study, year	Site (vessel cut off)	n	Stenosis (mean), %	Time of onset to Tx	Balloon	Stent	Complication	Restenosis	Dual antiplatelet duration	
									pre	post
Turk et al. [16], 2007	A1, A2, M1, P1 (≤ 2 mm)	4	>75	>5 days (N/A)	Maverick	NF (3) or WS (1)	none	1 (25%) (+S = 0)	5 days	indefinite
Xu et al. [15], 2009	P1 (<2.5 mm)	1	85	2.5 months	Jostent	Jostent	none	0	2 months	N/A
Hussain et al. [17], 2010	M2 (≤ 2 mm)	5	85–95 (90)	>1 day (N/A)	Gateway	none	none	2 (40%) (+S = 2)	≥ 1 day	3 months
Zhang et al. [14], 2012	ICA, M1/M2, PC (≤ 2.5 mm)	39	50–90 (73.9)	1–45 days (23)	Gateway	WS	1 (sICH)	13 (33.3%) (+S = 2)	3 days	6 weeks
Our study	A2, A3, M2, M3, P2, PC (≤ 2 mm)	10	55–95 (79.9)	3 days to 6 months (4.8 months)	Gateway	WS	none	1 (10%) (+S = 1)	3 days	indefinite when possible (6/10)

Jostent = Balloon-mounted bare metal stent (Abbot vascular, Germany); n = total number of patients; N/A = not available; NF = Neuroform stent (Boston scientific); PC = posterior circulation; +S = symptomatic in-stent restenosis; sICH = symptomatic intracranial hemorrhage; Tx = treatment; WS = Wingspan stent.

Discussion

It is estimated that up to 10% of all strokes in the US are due to ICAD [1]. Despite medical treatment, stroke recurrence can be as high as 18% within the first year for patients with severe stenosis ($\geq 70\%$) [4]. Recently, SAMMPRIS, the only randomized controlled trial for endovascular treatment of ICAD, demonstrated the superiority of aggressive medical therapy over PTAS, as stroke recurrence occurred within the first year in 12.2 versus 20.9% of patients in the medical and PTAS arms, respectively. SAMMPRIS studied ICAD only in large intracranial arteries (2–4.5 mm); unfortunately, small-artery ICAD has not been studied extensively, and endovascular treatment may be a valuable alternative in medically refractory patients as large- and small-artery ICAD could possibly represent two distinct entities, with a different natural history and response to medical and interventional treatments (table 2) [14–17].

In our study, all 10 patients had symptomatic small-artery ICAD (mean stenosis of 79%) refractory to medical therapy, and treatment with either primary balloon angioplasty or PTAS (Wingspan Stent System) yielded a 100% technical success rate. This is comparable with other small-artery ICAD studies with reported success rates of 98.1–100%, with the only technical difficulty due to failure of Wingspan stent deployment in a tortuous M2 lesion [14–17]. Furthermore, there were no periprocedural complications in our patients, which is also similar to previously published case series (table 2). This could partially be explained by patient selection and operator experience with the Wingspan Stent System. In SAMMPRIS, about a third of periprocedural complications (symptomatic intracranial hemorrhage) were due to reperfusion injury or wire manipulation-related dissections which have been postulated to be related to operator inexperience with the Wingspan Stent System in some of the low-volume centers; it has also been previously shown that mastering the Wingspan Stent System has a significant learning curve [18].

Another important aspect is the post-intervention restenosis rate, which directly affects clinical outcome. The mechanism of restenosis after angioplasty or stenting is not well known. Factors like post-instrumentation, remodeling, vascular contraction, and/or inflammation are hypothesized [19, 20]. Some of the risk factors for in-stent restenosis (ISR) include rapid balloon inflation, stent under-sizing, lesion length, diameter, and location (ISR occurs more frequently in the anterior circulation arteries) [21–24]. In this study, only 1 patient had restenosis (case 2.1; table 1), which occurred 1 month after primary angioplasty. The patient was retreated with PTAS with no further in-stent restenosis during follow-up. In other small-artery ICAD publications, the overall restenosis rate for primary angioplasty was 40.0% (all

symptomatic) and 27.7% for PTAS (only 5.6% symptomatic) [14–17]. Studies examining large-artery ICAD have stated a variable in-stent restenosis rate for the Wingspan Stent System. The in-stent restenosis rate has been reported to be 7.5, 25 (3.8% symptomatic), and 34.5% (9.5% symptomatic) in the Humanitarian Device Exemption (HDE) study, NIH Multi-center Wingspan registry, and US Wingspan registry, respectively [7, 11, 25, 26]. It is important to note that the majority of in-stent restenosis in patients treated for large-artery ICAD is asymptomatic. Additionally, in a meta-analysis of large-artery ICAD literature (1980–2008), a comparison of primary angioplasty versus PTAS treatment showed a trend for better outcome in patients treated with PTAS as both stroke incidence within the first year (19.7 vs. 14.2%, $p = 0.009$) and restenosis rate (14.2 vs. 11.1%, $p = 0.04$) were significantly lower in the PTAS group [27].

Lastly, in our study, all patients demonstrated good functional outcome on follow-up (mean of 18.6 months) with either a mRS of 0 or 1. Unfortunately, functional outcome has not been consistently reported in other small-artery ICAD studies [14–17].

Limitations for this study include its retrospective data collection, selection bias, and small sample size.

Conclusion

Small-artery ICAD is an important cause of stroke and, given its poor natural history, there is an urgent need for alternative treatments for medically refractory patients. Endovascular treatment of small-artery ICAD is technically challenging given the small lumen size, tortuosity, and thin smooth muscle of small arteries; however, the advent of newer devices specific for distal cerebral arteries has made angioplasty and stenting possible. In this study, we showed that endovascular treatment of small-artery ICAD in a high-volume center could be both safe and effective in patients refractory to medical management. Although limited, current evidence demonstrates a trend for efficacy of endovascular treatment in small-artery ICAD, which may provide support for a randomized controlled trial.

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