Applications of stenting for intracranial atherosclerosis

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Intracranial atherosclerosis presents a therapeutic challenge to medical and surgical physicians alike. Despite maximal medical therapy, the stroke rate from this disease is still high, especially when arterial stenosis is severe and patients are symptomatic. Open surgical therapy has yet to be shown to be a more efficacious treatment than medical therapy alone, largely due to the relatively high rates of perioperative complications. Angioplasty has a similar fate, with the risk of periprocedural complications outweighing the overall benefit of treatment. With the advent of stents for use in intracranial vasculature, new hope has arisen for the treatment of intracranial atherosclerosis. The NEUROLINK system, the drug-eluting stents Taxus and Cypher, the flexible Wingspan stent, the Apollo stent, and the Pharos stent have all been used in various prospective and retrospective clinical studies with varying technical and clinical results. The authors’ objective is to review and loosely compare the data presented for each of these stenting systems. While the Wingspan stent appears to have somewhat of an advantage with regard to technical success in comparison with the other stenting systems, the clinical follow-up time of its studies is too short to properly compare its complication rates with those of other stents. Before we continue to move forward with stenting for intracranial stenosis, a randomized prospective trial is ultimately needed to directly compare intracranial stenting to medical therapy.

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Key Words • intracranial arteriosclerosis • stent • stroke

Abbreviations used in this paper: MCA = middle cerebral artery; TIA = transient ischemic attack; WASID = Warfarin-Aspirin Symptomatic Intracranial Disease.

NEUROLINK Stent

Although the NEUROLINK System (Guidant Corp.) is no longer in use, it was initially approved by the FDA under a Humanitarian Device Exemption in 2002 and was the first of many intracranial stents studied for the treatment of intracranial atherosclerosis. A multicenter, nonrandomized prospective trial named SSYLVIA (Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries) tested the flexible, balloon-mounted NEUROLINK stent, composed of 316 L stainless steel, in 61 patients with at least 50% symptomatic stenosis of the extracranial vertebral arteries or intracranial arteries. Of the 61 treated arteries, 18 (30%) were extracranial vertebral and 43 (70%) were intracranial. Technically successful stent deployment occurred in 58 patients (95%), and procedural success, defined by study parameters as less than 50% poststent stenosis, occurred in 54 patients (89%). At 30 days, no deaths and 4 strokes (7%) were observed. One of the strokes was a subarachnoid hemorrhage that did not result in any neurological deficits, while the other 3 were major ipsilateral strokes. All 3 of the ischemic strokes were of the posterior circulation.

At 6-month angiographic follow-up, significant restenosis greater than 50% was detected in 18 patients (30%). Of the 37 stented intracranial arteries, 12 (32%) exhibited significant restenosis, and of the 14 stented extracranial
vertebral arteries, 6 (43%) exhibited significant restenosis. Symptomatic restenosis, stroke, or TIA was present in 7 (39%) of the 18 patients with significant restenosis at follow-up. Fifty-five patients returned for 1-year clinical follow-up, during which time an additional 4 patients (7%), not including the 4 patients who had strokes within the first 30 days, experienced strokes in the distribution of the treated stenotic vessel resulting in 1 death. Two of the 4 delayed strokes were of the anterior circulation, and the other 2 were of the posterior circulation. Cumulatively, 6 (75%) of 8 strokes documented within 1 year were of the posterior circulation, which correlates with the higher stroke rate seen in vertebrobasilar stenosis when compared with intracranial stenosis of the anterior circulation.23 Despite these initial results, further studies with the NEUROLINK stent were not conducted, perhaps due to advances in stent technology that were developed shortly after these data were published.

### Drug-Eluting Stents

The introduction of drug-eluting stents greatly decreased the restenosis rate of coronary artery stents in the treatment of coronary artery disease.13,28 In an attempt to duplicate those reductions in restenosis in the treatment of intracranial atherosclerosis, Abou-Chebl et al.1 treated a small series of patients by placing balloon-mounted, drug-eluting stents in the intracranial arteries. This was the first published series describing the use of drug-eluting stents in humans after an initial study of sirolimus-coated Cypher stent (Cordis Corp.) deployment in canine basilar arteries showed promising results.21 The group prospectively selected 8 patients with symptomatic intracranial stenosis that was greater than 70% and refractory to medical management. The authors used coronary drug-eluting stents to treat the patients’ diseased vessels. Half of the patients received the Cypher stent and the other half received the paclitaxel-coated Taxus stent (Boston Scientific). There were 2 periprocedural complications (25%), one (12.5%) of which was symptomatic but unrelated to the stent, being a retinal embolism during guide catheter removal. The mean preprocedural stenosis of 84.4% was reduced to a mean postprocedural stenosis of 2.5%. At a mean clinical follow-up of 11 months, there were no recurrent ischemic events. Of the 5 patients with a mean angiographic follow-up of 10 months, none had significant (> 50%) restenosis. Notably, only 1 patient showed any degree of restenosis with 29% stenosis on imaging at 12.6-month follow-up. While the number of patients was too few to make any generalized statements, this study showed the viability and safety of drug-eluting stents in a carefully selected patient set.

A second study with similar patient selection criteria (that is, their conditions were symptomatic and refractory to medical treatment with at least 50% stenosis of the affected intracranial artery), also examined the technical feasibility and restenosis rates of the same 2 drug-eluting stents, Cypher and Taxus, for the treatment of intracranial atherosclerosis.24 Of the 21 patients in whom stent placement was attempted, technical success was achieved in 18 (86%) with a reduction in mean stenosis from 68% preproce-
within 72 hours posttreatment showed 13 new ischemic lesions (34%), 3 (8%) of which were symptomatic. Including those 3 symptomatic patients who had new imaging findings, a total of 5 (6%) of the 78 treated patients had periprocedural complications, including 4 deaths (5%). One of the deaths occurred during a procedure in which the basilar artery was perforated by the guidewire. The other 3 deaths occurred on postprocedural Days 5, 15, and 16. The overall results from this preliminary study showed an impressively high technical success rate accompanied by an acceptably low complication rate, indicating that the Wingspan stent was a marked improvement over its predecessors.

Shortly thereafter, a prospective, multicenter study using the Wingspan stent with intermediate follow-up selected 45 symptomatic patients whose conditions were refractory to medical therapy with at least 50% stenosis of an intracranial vessel of a caliber 2.5–4.5 mm.2 Technical success was achieved in 44 patients (98%) with a reduction in vessel stenosis from a mean of 75% to a mean of 32% posttreatment. Two patients (4%) had large ipsilateral strokes and died within the first 30 days. At 6-month clinical follow-up, 2 more patients had strokes, one ipsilateral and the other contralateral, for a cumulative combined stroke or death rate of 9% (4 of 45). Further physician-reported outcomes outside of the study protocol at an average of 13 months posttreatment showed another patient with an ipsilateral stroke. At 6-month angiographic follow-up in 40 patients, the mean stenosis of 28% was not significantly different from the degree of stenosis immediately after stent deployment. However, 3 patients (7.5%) had significant restenosis of at least 50% at follow-up, all of whom were asymptomatic. Additional procedural adverse events included vasospasm in 5 patients and MCA branch occlusion in 1 patient without any permanent clinical sequelae. Four access site complications, including 3 hematomas and 1 infection, required further treatment, but all ultimately resolved. This study was limited by the number of enrolled patients and its relatively short follow-up time, but it made a strong case for the potential benefits of Wingspan stent treatment of symptomatic intracranial atherosclerosis in which medical therapy failed. A later study by Levy et al.32 in a similar group of patients reported a higher rate of in-stent restenosis of approximately 30% compared with 7.5% and a higher rate of symptomatic restenosis of 7% compared with none. While symptomatic restenosis unarguably warrants treatment, the lack of long-term outcome data on asymptomatic restenosis makes it a much murkier clinical scenario.

The WASID study showed that decreased time from qualifying clinical event to study enrollment and a high degree of stenosis were powerful predictors of stroke in the territory of the stenotic artery.3 The 1-year territorial stroke rate was higher in patients who had their qualifying events less than 30 days from study enrollment (23%) than in patients who had their events more than 30 days from study enrollment (10%). Not surprisingly, patients with severe arterial stenosis (≥70%) had a higher 1-year territorial stroke rate (18%) than patients without severe arterial stenosis (7%). Zaidat et al.30 enrolled 129 patients with severe intracranial stenosis (≥70%) for endovascular treatment with the Wingspan stent and followed their outcomes for 6 months. This study had a 97% technical success rate with a significant immediate postprocedural increase in the arterial diameter, from 82% preprocedural to 20% postprocedural mean arterial stenosis. Angiographic follow-up was obtained in 52 patients (40%) and showed restenosis of at least 50% in 13 patients (25%). Of those patients with significant restenosis, only 2 (15%) were symptomatic. Eight patients in the study (6%) had periprocedural (<24 hours) events, defined as any stroke or death. The 2 patients who died both suffered from pontine strokes, one ischemic and the other hemorrhagic. At 30 days, a total of 12 patients (9%) had events, including 4 deaths, and at 6 months, the cumulative event rate was 14%. While the results from this study were not as impressive as its predecessor’s, the discrepancy was likely due to the greater degree of neurovascular compromise in this study’s patients. Like its predecessors, this study was limited by its lack of long-term follow-up but again demonstrated the Wingspan stent to be effective at its job description.

A recently published single-center, retrospective study by Guo et al.12 looked at the application of the Wingspan stent specifically for MCA stenosis which, due to the structure and location of the MCA, is often a technically demanding disease to treat. Building on previous smaller studies of other stenting systems for MCA stenosis that showed high technical success rates and reasonably low complication rates,16,20 the authors hypothesized that the more flexible Wingspan stent would be able to face the challenges presented during stenting of the proximal MCA and ultimately improve clinical outcomes. The study enrolled 53 patients with at least 50% stenosis of the M1 segment of the MCA who were symptomatic despite standard medical therapy. The procedure was technically successful in 52 (98%) of 53 patients, reducing the mean pretreatment stenosis of 77% to a mean 18.2% posttreatment stenosis. Including the 1 technical failure, 4 patients (7.5%) experienced complications, 2 (4%) of which resulted in permanent neurological deficits. Among the 32 patients with angiographic follow-up at 6 months, none had significant restenosis greater than 50%. All 52 patients who underwent successful stenting were clinically evaluated at 6 months and received transcranial Doppler ultrasonography measurements of MCA flow velocities. The relatively short follow-up limits our ability to assess possible delayed in-stent stenosis or other long-term complications, but nonetheless this study certainly supports for the technical capabilities of its interventionalists and the versatility of the Wingspan stent.

**Apollo Stent**

The Apollo stent (MicroPort Medical) is a balloon-mounted, flexible 316 L stainless-steel stent device that was tested by Jiang et al.31 in a single-center prospective trial. The study enrolled 46 patients with 48 intracranial arterial stenoses greater than 50% on angiography. The stenoses were symptomatic, defined as TIA’s or minor strokes within 90 days of stent placement. Technical success was achieved in 42 patients (91%) with all 4 failures attributed to tortuosity of the target stenotic vessel. At 30 days, 4 (9%)
of the 46 patients experienced strokes, 3 (7%) of which were symptomatic due to perforating artery compromise on postprocedure Day 1. All patients were available for a median follow-up of 24 months. After 30 days, 1 patient had a stroke in the distribution of the stented artery, and 2 patients had ischemic strokes in an untreated arterial distribution. A total of 6 (14%) of the 42 patients who were successfully treated had strokes within the clinical follow-up period. Of the 25 patients who underwent angiographic follow-up at a median time of 7.4 months, 7 patients (28%) had restenosis of the treated vessel, resulting in 1 symptomatic restenosis (4%). While the study was underpowered to detect a statistically significant advantage of stenting over medical therapy, it did show that the Apollo stent has the potential to be effective in the treatment of symptomatic intracranial atherosclerosis given good preprocedural selection. Not surprisingly, the likelihood of technical failure increased with increasing target vessel tortuosity, although technical success surely depended on the biomechanical limitations of the device itself along with the skill and expertise of the operators.

**Pharos Stent**

Derived from a coronary stent, the balloon-mounted Pharos stent (Micrus Endovascular), previously known as the Lekton Motion stent, showed some promise of future success in 2 small studies. The first, a retrospective multicenter study by Freitas et al., examined the efficacy of the Pharos stent in 32 patients with at least 50% intracranial stenosis, all of whom were symptomatic despite medical therapy except 2 asymptomatic patients. Technical success was achieved in 31 patients (97%) with 2 periprocedural complications (6%), one of which was symptomatic. Immediate postprocedural results showed complete stenosis reduction in 24 patients (75%) and partial reduction in 8 patients (25%) to less than 20% residual occlusion. At 30-day clinical follow-up, including the immediate postprocedural events, 5 patients (16%) suffered stroke or died. Of the 3 deaths (9%), 2 were attributed to medication noncompliance, leading to stent thrombosis and multisystem failure following a hypertensive episode while the cause of death of the third patient was unknown. At a mean clinical follow-up of 10 months, no additional strokes or deaths were reported. At mean angiographic follow-up of 10 months in 23 patients, 3 patients (13%) had significant restenosis greater than 50% while 1 patient (4%) had nonsignificant restenosis of less than 10%; all were asymptomatic. The average poststenosis stenosis at angiographic follow-up was 5%, down from an average 69% prestent stenosis. This initial study demonstrated the technical feasibility and short-term viability of the Pharos stent, although the 30-day mortality rate, which may have been a consequence of patient selection, was higher than that in other comparable studies.

A second single-center study out of Germany enrolled 21 symptomatic patients with at least 70% intracranial arterial stenosis for treatment with the Pharos stent. Interestingly, 7 (33%) of these patients were treated in the setting of an acute stroke. Technical success was achieved in 19 patients (90%); both treatment failures were due to complex courses of the stenotic vessels. One of these patients was subsequently successfully treated with 2 Wingspan stents. Both technical failures occurred in the electively treated cohort. The reduction in median stenosis was from 85% pretreatment to 20% posttreatment. Within the first 30 days after stent placement, 4 (29%) of the 14 electively treated patients experienced complications, 2 (14%) of which resulted in permanent neurological sequelae. One of the patients had a major stroke despite subsequent open surgical bypass. Another patient who received a basilar artery stent had a minor stroke of a pontine perforator. For the 2 patients who did not have permanent deficits, one experienced immediate postprocedural stent thrombosis that resolved with endovascular recanalization and the other suffered a brainstorm TIA with complete clinical recovery after 24 hours. One of the patients died at 3 months for a total of 3 electively treated patients (21%) who suffered a stroke or died at a mean clinical follow-up of 7 months. Of the 7 patients urgently treated for acute strokes, 2 (29%) died within the first 30 days and another 2 patients went on to develop strokes by a mean clinical follow-up of 10 months for a cumulative stroke or death rate of 57% in the urgently treated group. Despite the small number of patients in the urgently treated cohort, it is apparent from this study that stenting in the setting of acute stroke is extremely risky and warrants thorough consideration before being undertaken.

**The Future of Stenting for Intracranial Atherosclerosis**

Gröschel et al. performed a meta-analysis of 31 studies involving 1177 procedures for high-grade (mean 78%) symptomatic (98%) intracranial arterial stenosis. The outcomes varied widely across the studies with procedural success rates ranging from 71% to 100%, periprocedural complication rates ranging from 0% to 50%, and restenosis greater than 50% ranging from 0% to 50%. The rate of periprocedural stroke or death was significantly higher (p = 0.006) in the treatment of posterior circulation stenosis (12.1%) than in the treatment of anterior circulation stenosis (6.6%). The rate of periprocedural complications did not differ (p = 0.470) between treatments with balloon-mounted (9.5%) and self-expandable (7.7%) stents. The clinical follow-up after the procedures ranged from 3 to 21 months with a median follow-up of 6 months. The total restenosis rate was 14.4%, of which 32.7% were symptomatic, that is, TIA, stroke, or death. While there was a statistically significant difference (p < 0.001) in any restenosis between treatment with balloon-mounted (13.8%) and self-expandable (17.4%) stents, there was no statistically significant difference (p = 0.080) in symptomatic restenosis between the 2 treatments (41.6% [balloon-mounted] vs 12.5% [self-expandable]). The cumulative probability of stroke or death was approximately 12%, indirectly comparable to that of medical therapy in the WASID study. Based on these data, there is not a strong argument for or against the benefit of endovascular stenting therapy over conventional medical therapy for the treatment of intracranial stenosis. However, the lack of a prospective randomized trial comparing the 2 therapies makes it difficult to draw a definitive conclusion.
Applications of stenting for intracranial atherosclerosis

Table 1 compares the technical success rates immediately after the procedure and the complication rates at clinical follow-up across different stents. The Wingspan stent can be seen to have the highest technical success rates, likely due to its more flexible nature when compared with its counterparts. While the Wingspan stent does also appear to have lower complication rates, the mean clinical follow-up for those studies is shorter, making the comparison somewhat uneven. Another obvious confounding factor is that since the operators in each trial are different, their experience and skill levels are obviously not the same. We can safely assume that all of the interventionalists are skilled, but their experiences with the individual stents may have varied considerably, making it difficult to compare stents across different studies. However, the question that looms the largest after all of these studies is whether the complications associated with stenting are justified by the benefits. Without a prospective, 2-arm study that directly compares stenting to medical therapy, we cannot answer fairly.

As device delivery and stent technology continue to improve at an explosive rate, it is difficult to make direct comparisons between the different types of stents. Balloon-mounted stents are typically much stiffer and harder to deliver through tortuous anatomy than self-expanding stents, but they only require crossing the lesion once. Self-expanding stents, while flexible and potentially easier to deliver, typically require crossing the lesion with 2 devices, the first being a balloon used for predilation followed by the stent, theoretically increasing the chance of incurring a thromboembolic event. As alloy composition, stent architecture, and device maneuverability continue to improve, technical success and complication rates between stents will likely blur into one another. In Fig. 2, we show an example of a patient with proximal MCA atherosclerosis who was successfully treated at our institution with a balloon-mounted coronary stent.

Given the FDA approval of the Wingspan stent under a Humanitarian Device Exemption supported by initial studies demonstrating its high technical success rate and good safety profile and data showing that severe, symptomatic intracranial atherosclerosis portends a poor prognosis despite maximal medical therapy, a well-conceived randomized trial prospectively comparing stenting with standard medical management has the potential to establish landmark clinical guidelines in stroke treatment.6 The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial is currently recruiting with

<table>
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<tr>
<th>Stent</th>
<th>Authors &amp; Year</th>
<th>Min Stenosis (%)</th>
<th>No. of Pts</th>
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<th>Restenosis Rate &gt;50% (%)</th>
<th>Tech/Procedural Complication Rate (%)†</th>
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* Asymp = asymptomatic; FU = follow-up; Min = minimum; Pts = patients; Tech = technical.
† Technical/procedural complications may overlap with asymptomatic and symptomatic stroke and death. The cumulative complication rate is the total of asymptomatic and symptomatic stroke and death rates only and does not include technical/procedural complications that did not result in stroke or death.
‡ Eighteen of 61 treated patients had extracranial atherosclerosis.
§ The patients in this study were treated only for M1 stenosis.
¶ Seven of the 21 patients were treated in the setting of acute stroke, 4 of whom had complications.

Fig. 2. Angiograms obtained in a patient at our institution with severe right M1 segment MCA stenosis (left, arrow) that was successfully stented with a balloon-mounted coronary stent (right). Note the improved flow in the MCA circulation after stent placement as evidenced by increased filling of the distal MCA branches relative to the anterior cerebral artery branches.
a goal of 764 patients at 60 academic and community centers across the US (http://www.sammpris.org/). Its inclusion criteria include, but are not limited to, patients 30–80 years old with a modified Rankin Scale score not greater than 3 who experience a TIA or minor stroke fewer than 30 days prior to enrollment, attributable to at least 70% stenosis but less than 100% occlusion of a major intracranial artery (carotid, M1, vertebral, or basilar) diagnosed by transcranial Doppler ultrasonography, MR angiography, or CT angiography, and confirmed by subsequent catheter angiography. The enrollees will be randomized into one of 2 arms, either medical therapy alone or intracranial stenting plus medical therapy, and will be followed clinically for 1–3 years. Medical therapy, as defined by the SAMMPRIS study parameters, is aspirin 325 mg daily for the entire course of enrollment, clopidogrel 75 mg daily for 90 days following enrollment, and aggressive blood pressure and cholesterol management by each study center neurologist to keep the blood pressure lower than 140/90 mm Hg and lower than 130/80 mm Hg in patients with diabetes and low-density lipoprotein cholesterol less than 70 mg/dl. We eagerly await the results of this trial and anticipate that its conclusions will be of great importance to stroke neurologists and neurointerventionalists alike.

Conclusions

The role of intracranial stenting in the treatment of intracranial stenosis, the management of its complications, and the long-term clinical and angiographic effect it affords patients has yet to be fully delineated. However, stenting has been clearly shown to be a versatile weapon in our ever-expanding arsenal of therapeutic strategies for a disease with potentially devastating consequences. While some studies have shown promising results, we are limited by the lack of prospective, randomized controlled data directly comparing intracranial stenting to standard medical therapy. Until such results are available, we can continue to be cautiously optimistic that the use of intracranial stents will reduce the acute and chronic morbidity and mortality of intracranial atherosclerosis.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors.

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