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ABSTRACT

BACKGROUND AND PURPOSE: Different types of symptomatic intracranial stenosis may respond differently to interventional therapy. We investigated symptomatic and pathophysiologic factors that may influence clinical outcomes of patients with intracranial atherosclerotic disease who were treated with stents.

MATERIALS AND METHODS: A retrospective analysis was performed of patients treated with stents for intracranial atherosclerosis at 4 centers. Patient demographics and comorbidities, lesion features, treatment features, and preprocedural and postprocedural functional status were noted. χ^2 univariate and multivariate logistic regression analysis was performed to assess technical results and clinical outcomes.

RESULTS: One hundred forty-two lesions in 131 patients were analyzed. Lesions causing hypoperfusion ischemic symptoms were associated with fewer strokes by last contact [χ^2 (1, n = 63) = 5.41, P = .019]. Nonhypoperfusion lesions causing symptoms during the 14 days before treatment had more strokes by last contact [χ^2 (1, n = 136), 4.21, P = .047]. Patients treated with stents designed for intracranial deployment were more likely to have had a stroke by last contact (OR, 4.63; P = .032), and patients treated with percutaneous balloon angioplasty in addition to deployment of a self-expanding stent were less likely to be stroke free at point of last contact (OR, 0.60; P = .034).

CONCLUSIONS: More favorable outcomes may occur after stent placement for lesions causing hypoperfusion symptoms and when delaying stent placement 7–14 days after most recent symptoms for lesions suspected to cause embolic disease or perforator ischemia. Angioplasty performed in addition to self-expanding stent deployment may lead to worse outcomes, as may use of self-expanding stents rather than balloon-mounted stents.

ABBREVIATIONS: BMS = balloon-mounted stent; ICAD = intracranial atherosclerotic disease; PTA = percutaneous transluminal angioplasty; SES = self-expanding stent

Intracranial atherosclerotic disease (ICAD) causes considerable morbidity and mortality, accounting for up to one-third of ischemic strokes in some series, particularly in certain populations.[1-3] Some lesions prove recalcitrant to first-line medical management, and, in recent decades, endovascular treatments have emerged and evolved as complementary therapies.[4,5] Early series demonstrated technical feasibility and acceptable safety for percutaneous transluminal angioplasty (PTA) and then stent placement of lesions in ICAD.[5-17] Initially, intracranial procedures were performed with devices designed and approved for coronary interventions, with subsequent release of angioplasty balloons specifically engineered for intracranial use.[5,12,17-33] In 2005, the Wingspan stent system with Gateway PTA balloon catheter (Stryker, Kalamazoo, Michigan) became the first stent approved for treatment of ICAD in the United States.[5,12,18-22,25,34] Numerous studies reported progressively improved outcomes and low complication rates, but randomized data proving efficacy were lacking.[5,12,18,20,24,25,35,36] In 2011, enrollment in the first randomized, controlled trial to evaluate stent placement versus medical management of ICAD, the Stent placement and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, was halted early due to

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high complication rates in the stent placement group as compared with the medical management group.[4]

The results of SAMMPRIS have elicited strong responses from both proponents and detractors of stent placement, with clinical decisions now changing.[5] This current study retrospectively analyzes results of stent placement procedures performed for ICAD at 4 centers, with attention given to factors not specifically assessed in SAMMPRIS that may help guide further investigations of endovascular ICAD management.

MATERIALS AND METHODS

Under institutional review board–approved protocols, medical records were retrospectively examined by querying prospectively maintained procedure data bases at 2 large academic medical centers and 2 affiliated community hospitals, all of which have high-volume neurointerventional services. All patients who received stents for ICAD were evaluated. Patients with ICAD in whom stent placement was attempted but unsuccessful were included, as were patients with ICAD in whom PTA alone was planned but who received a stent to treat complications from PTA. Stent placement procedures performed during treatment of acute stroke were not included.

Information was gathered according to the guidelines of the Standards Committee of the Society for NeuroInterventional Surgery for investigations of endovascular treatment of ICAD.[5] Presenting symptoms were noted and, as appropriate, further classified as "hypoperfusion" if clear evidence existed that reduced perfusion elicited ischemic symptoms. Examples of sufficient evidence of hypoperfusion etiology included reduced flow demonstrated on perfusion imaging, infarcts clearly located in a watershed distribution, and symptom exacerbation during known hypotension or on application of positional stressors. Symptoms that were probably caused by mixed subtypes were classified as indeterminate, as were symptoms that could not be clearly classified as hypoperfusion or nonhypoperfusion. Among nonhypoperfusion lesions, further classification divided them according to the duration of symptom-free interval before treatment. Ischemic symptoms were classified as TIA or stroke, the latter designated with permanent deficits or restricted diffusion on MR imaging. Specific medical comorbidities were considered present if a patient was treated for that condition; in the absence of treatment, the absence of a diagnosis was confirmed with clinical or laboratory data. Pretreatment antiplatelet or anticoagulation therapy other than procedural loading doses was noted. Functional status was evaluated by use of mRS, with a value assigned by authors performing data review on the basis of descriptions of functional performance in the medical record if a value was not formally noted.

The date of stent placement procedure and anesthesia type were recorded. Lesions were classified by vessel and furthest downstream vessel segment treated, listed in On-line Table 1. Lesion features and technical success were recorded according to those reported by the primary interventionalist, if available. When not explicitly stated, these data were assessed by investigators conducting data review. The degree of stenosis was determined by use of the Warfarin-Aspirin Symptomatic Intracranial Disease Trial (WASID) technique.[5,37] Stenosis length was measured, and Mori classification was assigned.[38] The presence of tandem stenoses was noted, including stenoses in upstream extracranial vessel segments. Stent type, model, size, and number deployed were noted, as was performance of PTA during the same procedure. Postdeployment stenosis was measured in the same fashion as measurement before deployment. Technical success was defined as residual stenosis $<$50% without procedural complication.[5] Any procedural complications were noted, as well as means taken to treat them, if applicable, and whether such complications were symptomatic. Complications occurring after procedure completion within 30 and 90 days of treatment were classified as peri-procedural and post-procedural, respectively.

The duration for postprocedure treatment with aspirin and clopidogrel was noted, as were use of glycoprotein IIb/IIIa inhibitors or any combination antiplatelet agents. Follow-up interval and duration were determined by the primary interventionalist, as was the technique of any follow-up imaging; no formal protocol existed between practitioners. The most recent date of contact was determined for long-term follow-up. For those patients with available records, the Social Security Death Index was queried to screen for deaths among patients lost to follow-up.[39] In patients who died, death records were reviewed to evaluate cause of death.

End points evaluated were ischemic stroke, intraparenchymal hemorrhage, death, or other adverse event related to treatment at 30 days, 90 days, 1 year, 2 years, and point of last contact. Functional status was also assessed at these time points with the use of mRS. Data analysis was performed with the use of χ^2 tests and logistic regression analysis by use of IBM SPSS version 20 (IBM, Armonk, New York).

RESULTS

Between June 1998 and December 2011, 142 lesions in 131 patients met inclusion criteria and had sufficient medical records for review. All sites in this study participated in the SAMMPRIS trial, but the few enrolled patients did not have data sufficient for inclusion in this study. Patient demographics, symptom features, and lesion characteristics are summarized in On-line Table 1. Technical success was achieved in 124 (87.3%) procedures. Treatment details and angiographic results are summarized in Table 1. Procedural complications occurred during treatment of 13 (9.2%) lesions, with 2 complications occurring during 1 procedure for the same lesion. Of these complications, two (1.4%) caused neurologic symptomatic sequelae. No permanent nonneurologic morbidity occurred from procedural complications. Mean follow-up time was 949 days (standard deviation, 1187; median, 413). Follow-up time exceeded 90 days for 101 (71.1%) lesions and 1 year for 79 (55.6%) lesions. Eighteen complications occurred in the postprocedural period, of which 13 were symptomatic. Thus, overall postprocedural complications occurred in 34 (23.9%) cases, with complications causing permanent symptomatic sequelae in 16 (11.3%) cases, summarized in On-line Table 2.

No difference was noted in outcomes when comparing symptom types. Head-to-head comparison of hypoperfusion and nonhypoperfusion lesions showed correlation of the latter

Table 1: Treatment characteristics

No. of stents deployed			
0	6		
1	136		
2	10		
Stent modalities			
Balloon-mounted, bare metal	78		
Balloon-mounted, drug-eluting	21		
Self-expanding	47		
Total	146		
Anesthesia technique			
MAC	36		
GETA	106		
Stent types			
AVE Series	53		
Bx Velocity	11		
Driver	15		
Palmaz	2		
Wingspan	37		
Other[a]	28		
Total	146		
Stent-designed indications			
Coronary	95		
Neuro	40		
Peripheral	11		
Total	146		
Angiographic results			
Mori	Pretreatment stenosis	Posttreatment stenosis	Success
A ($n = 19$)	80.8%	3.9%	84.2%
B ($n = 73$)	80.2%	7.8%	89.0%
C ($n = 50$)	86.0%	13.8%	86.0%

Note:—MAC indicates monitors anesthesia care; GETA, general endotracheal anesthesia.
[a]Cypher, Enterprise, Herculink, Multi-Link, Neuroform, NIR Primo, Precise, Sprint, Taxus.

Table 2: Multivariate models

	OR	95% CI	*P* Value
mRS >2 at last contact			
Tandem	0.319	0.143–0.713	.005
Hyperlipidemia	3.158	1.220–8.173	.018
Antiplatelet	3.907	1.107–13.792	.034
Tobacco	0.437	0.197–0.968	.041
Death at last contact			
Tandem	0.297	0.111–0.799	.016
Antiplatelet	4.504	1.017–19.949	.047
Diabetes	0.432	0.175–1.065	.068
PTA SES	4.028	0.875–18.532	.074
Tobacco	0.451	0.185–1.099	.080
Sex	2.285	0.649–8.042	.198
Neuro stent	1.725	0.393–7.565	.470

with new or recurrent stroke by last contact [χ^2 (1, $n = 63$) = 5.41, $P = .019$]. Nonhypoperfusion lesions causing symptoms within 7 days of treatment were associated with stroke by last contact [χ^2 (1, $n = 136$), 4.21, $P = .047$]. When considering nonhypoperfusion lesions causing symptoms within 14 days, the association was stronger [χ^2 (1, $n = 136$) = 4.93, $P = .032$]. A trend was also noted for nonhypoperfusion lesions being correlated with complications occurring in the first 90 days after treatment, though this did not reach statistical significance [χ^2 (1, $n = 68$) = 3.68, $P = .051$].

The results of univariate analysis are summarized in Online Tables 3–9. Adverse events were more likely to occur in women and patients with diabetes, history of stroke, history of tobacco use, no diagnosis of hyperlipidemia, or no preprocedural antiplatelet therapy. Lesion features associated with death, stroke, or mRS >2 included basilar artery location, involvement of any basilar segment or petrous ICA, tandem lesions, Mori C classification, treatment with self-expanding stent (SES), and PTA performed in addition to SES deployment. Use of stents designed for intracranial use was associated with stroke, whereas stents designed for use elsewhere were associated with death.

In multivariate analysis (Table 2), patients treated with stents designed for intracranial deployment were less likely to be stroke free by last contact (OR, 0.060; 95% CI, 0.004–0.812; $P = .034$). This distinction did not predict rates of restenosis in this series. All 4 variables with statistically significant effects on mRS by last contact retained significance in the multivariate model. Absence of antiplatelet therapy and presence of tandem stenoses retained significance in prediction of death by last contact.

DISCUSSION

ICAD causes a significant burden worldwide, accounting for 10–15% of strokes in series published from the United States and up to 33% in series from Asia.[3,5,40] Many high-risk characteristics were demonstrated in the WASID trial, which also established the role for dual antiplatelet therapy in ICAD treatment, findings confirmed in this current study.[37,40] Since the WASID trial, standard of practice in medical management has undergone a paradigm shift toward aggressive medical management that also includes lifestyle modifications, a shift that has now been accentuated by SAMMPRIS.[5]

Despite advances in medical therapy, some patients' symptoms recur. It is these patients for whom surgical and endovascular therapies were initially developed. Initial operative treatments showed promise, but subsequent examination in large trials showed no benefit of surgical intervention.[41,42] Early endovascular treatment typically involved PTA alone, but residual stenosis >50% was common, and many patients had dissections that required stent placement.[1,5,14,15,43] PTA also carries a risk for arterial perforation and is often counteracted acutely by vessel recoil.[5] Thus, development of stent placement for ICAD was pursued.[5]

Initial reports demonstrated that intracranial stent placement can involve serious complications, dictating that such stents be used only in high-risk patients with medically refractory disease.[9,10] However, with advances in stent placement technique and technology, both technical success rates and complication rates improved.[5,24,25,44,45] On the basis of data from procedures with the use of devices designed for use in coronary arteries, technical success rates appeared to plateau around 95% with complications within the first 30 days after stent deployment occurring in approximately 7% of cases.[5]

The Wingspan system is the first device granted Food and Drug Administration approval for treatment of ICAD. Multiple series using this stent have been reported.[12,18,24,25,35,36] The 2 largest nonrandomized, prospective series evaluating the device are the United States Wingspan registry, which reported a technical success rate of 98.8%, and the NIH Wingspan registry, which reported a rate of 96.7%.[18,25] Restenosis >50% occurred in 27.9% and 25% of patients in these studies, respectively.[18,25] In the current series, technical success occurred in 87.3% of cases, and restenosis >50% occurred in 13.4%.

The peri-procedural complication rates of the 2 registries (6.1% and 9.6%) approached that seen elsewhere for series that used other devices.[18,25] Because of inconsistency in follow-up scheduling for this current retrospective study, 30-day outcomes were not consistently available. However, the comparable 90-day rate of any stroke and death was 14.8%. Excluding radiographic infarcts with no permanent symptomatic sequelae to most closely mirror outcomes measured in registries, the postprocedural complication was 11.3% in our series. By comparison, WASID did not report 90-day complications, but these end points occurred within 1 year in 15% of patients in the aspirin group.[37]

Given that nonrandomized series had suggested improving stent safety and efficacy, SAMMPRIS was disappointing when the trial was halted short of its planned enrollment size because of an unexpectedly high rate of stroke or death within 30 days of treatment in the stent placement (14.7%) versus medical arm (5.8%).[4] No significant difference was noted between the groups beyond 30 days of enrollment, and the 1-year rate of stroke or death was 20.0% versus 12.2%, respectively.[4] SAMMPRIS helped identify the path forward to identifying a role for safe, efficacious interventional treatment of ICAD, namely the reduction of peri-procedural complications through factors such as device improvement, peri-procedural blood pressure management, anesthetic techniques, and use of combination antiplatelet drugs. Additionally, appropriate patient selection criteria must be identified. Multiple factors must be considered in the design of the SAMMPRIS trial and its implications for future investigation.[46]

The SAMMPRIS trial made no distinction between pathophysiologic causes of symptoms. Our series shows that nonhypoperfusion lesions have higher risk of death at the point of last contact after stent placement. Additionally, multiple prior studies demonstrated that complication rates increase the sooner intervention is performed with relation to most recent symptoms, probably related to stability of atherosclerotic plaques.[10,22,40,47] We posit that such concerns relate to unstable plaques that would be expected to cause primarily nonhypoperfusion symptoms, for example, embolization distal to the plaque or perforator occlusion adjacent to the plaque. In the current study, lesions causing nonhypoperfusion symptoms within 7 or 14 days of treatment were associated with stroke by point of last contact. Intervention timing, particularly for thromboembolic lesions, should be studied further. Optimum management also must be determined for lesions that do not afford sufficient asymptomatic windows. Additionally, stenosis caused by non-ICAD pathologies responds differently to endovascular treatment, shown by poor outcomes in patients without diagnosis of hyperlipidemia.

Before release of the Wingspan device, stent deployment to treat ICAD often required use of devices designed for coronary interventions.[5] Treatment with a balloon-mounted stent (BMS) carries concern for dissection, vessel rupture, and recoil after deployment.[1,43] With SES, wall stress persists longer than with BMS, causing more pronounced inflammation that causes neovascularization and neointimal hyperplasia.[48] This may account for the higher rates of recurrent stenosis seen after treatment with SES compared with BMS, and it probably explains the lower rates of restenosis in this mixed SES/BMS study rather than the larger purely SES Wingspan studies.[1,5,48-50]

The choice of intracranial stent has historically been driven by balancing potentially higher risks of BMS against greater residual stenosis and recurrence rates with SES. In this study, lesions treated with SES had worse rates of both stroke and death. Lesions treated with PTA in addition to SES had worse outcomes compared with treatment with BMS or SES without PTA. This could easily reflect bias, because more severe lesions may be more likely to be treated additionally with PTA. Severe lesions are also more likely to have poorer outcomes, as seen with Mori class C lesions in this series and elsewhere.[1] This certainly bears further examination given that the technique used in SAMMPRIS required PTA before SES deployment. Interestingly, devices specifically designed for intracranial deployment had less favorable outcomes than other types. This may reflect reported operator difficulty with the Wingspan system.[47,51,52] Future development of a BMS for intracranial use may affect results.

Limitations of this study result from its retrospective design. A lack of prospectively developed protocols for describing patient symptoms limited the analysis, particularly when attempting to discern treatment subtypes. Inadequate capture within early postprocedure periods limited direct comparison to other investigations. Although this study benefits from many years of data, it includes patients treated with methods formerly considered appropriate but not currently standard of care. Finally, all symptom and functional assessment was performed retrospectively by reviewing clinical follow-up documentation rather than formal standardized assessment, and follow-up was not standardized.

SAMMPRIS indicates that aggressive medical management should be the first-line treatment for ICAD. Further investigation must determine what treatments to offer for persistent symptoms and which patients are candidates for such treatment. Additionally, better metrics should be pursued that account for the nuances of symptoms from these lesions that can dramatically affect patients' lives but are not adequately captured by scales such as mRS.[53] Randomized, controlled trials should be sought, and novel designs should be considered, such as group crossover or Bayesian enrollment, and any treatment performed outside such trials should be included in multicenter registries with standardized protocols to best evaluate outcomes.

CONCLUSIONS

ICAD causes significant morbidity and mortality. Treatment must begin with medical management, but certain patients will remain symptomatic despite aggressive measures. In such cases, a role for endovascular treatment remains undefined. The current study demonstrates that lesions causing symptoms as the result of reduced perfusion have more favorable outcomes after stent

placement, and lesions causing nonhypoperfusion symptoms respond more favorably to stent placement when treated after a 7- to 14-day asymptomatic period. Currently available stents designed for intracranial use, SES deployment, and PTA in conjunction with SES deployment were associated with worse outcomes in the present study and warrant further examination.

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