Durability of Endovascular Therapy for Symptomatic Intracranial Atherosclerosis

Mikael Mazighi, MD, PhD; Jay S. Yadav, MD; Alex Abou-Chebl, MD

Background and Purpose—Intracranial angioplasty and stenting are therapeutic options for patients with symptomatic intracranial arterial stenoses intractable to medical therapy. However, the long-term safety and clinical efficacy of these techniques are unknown. We sought to assess the long-term outcome and efficacy of these techniques.

Methods—Procedural data and 30-day outcomes were collected from patients treated with coronary balloons and stents for ≥70% atherostenoses. Clinical and radiographic follow-up data were obtained at 30 days, 6 months, 12 months, and yearly thereafter.

Results—Fifty-three patients (median age, 67 years; interquartile range [IQR], 58.75 to 75 years) with 69 arterial lesions were treated during a 7-year period. The technical success rate was 98.6% (68/69), with a reduction of the median percent stenosis from 85% (IQR, 70% to 95%) to 0% (IQR, 0% to 26%). In 76.8% (53/69) of the procedures, a stent was implanted. The 30-day death/stroke rate was 10.1% (7/69) with 1 death, and within a median follow-up of 24 months (IQR, 10.25 to 36.5 months), the transient ischemic attack or stroke rate reached 5.8% (4/69). Restenosis rate at 1 year was 15.9% (11/69) and was symptomatic in 18.2% (2/11). The restenosis rate was 50% for angioplasty (8/16) and 7.5% (4/53) for stenting (hazard ratio = 5.02; 95% CI, 1.22 to 20.68). Factors associated with restenosis were vessel size <2.5 mm (hazard ratio = 4.78; 95% CI, 1.35 to 16.93) and interventions performed in the setting of an acute stroke (hazard ratio = 6.36; 95% CI, 1.78 to 22.56).

Conclusions—Intracranial stenting may reduce the rate of recurrent ischemia in patients in whom medical therapy is unsuccessful and is probably more durable than angioplasty alone. (Stroke. 2008;39:1766-1769.)

Key Words: atherosclerosis ■ intracranial stenosis ■ stroke management

Intracranial stenting is still an investigational technique owing to the absence of controlled, randomized trials for evaluating this technique against medical therapy and, perhaps most important, to the lack of data on the durability of endovascular therapy. For some of these issues, the available data suggest that endovascular therapy with periprocedural complication rates of 5% to 10%2-8 compares favorably with the natural history of medically treated patients who may have an ≈22% annual risk of stroke.9 Data on the other issues remain scarce, and some controversy exists regarding the choice of the best endovascular technique (ie, primary angioplasty versus stenting). Furthermore, restenosis is an emerging issue in intracranial arteries with rates as high as 32%.2 To expand the available data on long-term clinical and imaging follow-up, we report a single-center experience of intracranial angioplasty and stenting in patients with symptomatic intracranial stenosis.

Patients and Methods

Patient Selection and Data Collection

We analyzed a consecutive series of patients included in an interventional database who were treated (between March 1999 and June 2006) with angioplasty or stenting for ≥70% symptomatic, intracranial atherosclerotic stenoses that failed medical therapy. Failure of medical therapy was defined as recurrent stroke or transient ischemic attack (TIA) despite adequate treatment with aspirin, clopidogrel, warfarin, or a combination thereof. Procedures performed within 14 days of a stroke were considered to be acute interventions and were differentiated from elective ones. All patients gave informed consent before treatment. The database and this study received institutional review board approval.

Periprocedural Medical Treatment

All patients were pretreated with 325 mg aspirin and 75 mg clopidogrel for at least 4 days before the intervention. In those patients treated acutely, a clopidogrel (300 to 600 mg) and an aspirin (325 mg) loading dose was given as soon as possible before the procedure, or during the procedure if thrombolysis was not performed. Unfractionated heparin was given to all patients intraprocedurally to achieve a target activated clotting time ≥250 seconds.

Interventional Technique

Via a transfemoral approach, a 70- to 80-cm 7F to 8F sheath was placed in the distal common carotid artery or proximal subclavian artery. A 6F guide catheter (Envoy, Cordis Corp) was then placed into the distal cervical internal carotid artery or vertebral artery at the C2 level. Interventions were performed with the following 0.014-inch wires: Synchro, Boston Scientific Inc; and Balance Middle...
Weight, Guidant-Abbott Vascular; 0.014-inch coronary balloon: Maverick, Boston Scientific Inc; and balloon-expandable stents: Multi-Link Rx, penta or tetra, or DUET, Guidant-Abbott Vascular; S670, Medtronic; Express 2, Boston Scientific Inc; Vision, Guidant-Abbott Vascular; Driver, Medtronic; Bx Velocity, Cordis; Cypher, Cordis; or Taxus, Boston Scientific Inc. Angioplasty was performed with a slightly (10% to 15%) undersized coronary balloon (Maverick, Boston Scientific Inc) and with slow inflation. Stenting was performed when dissection, residual stenosis, or lesion recoil occurred. Stents were sized to match the diameter of the smallest normal arterial segment into which they were to be implanted.

Postprocedural Management
Heparin anticoagulation was immediately reversed in all patients postprocedurally. Patients were continuously monitored by frequent neurologic examinations and arterial blood pressure monitoring. Systolic blood pressures were kept at ≤140 mm Hg, except for those patients who were at risk of cerebral hyperperfusion (ie, recent symptoms, hypertension, poor collateral flow, or impaired cerebrovascular reserve); systolic blood pressures of these patients were kept at ≤120 mm Hg, even after discharge, for a minimum of 14 days. A regimen of 325 mg aspirin lifelong and 75 mg clopidogrel daily for 1 year if a drug-eluting stent [DES] was implanted) was given. Patients were evaluated by a board-certified stroke neurologist (not involved in the interventions) before and after the procedure and had follow-up visits at 30 days, 6 months, 12 months, and yearly thereafter. For patients who were unable to return to the clinic for follow-up, their clinical status was assessed in consultation with a local neurologist or by telephone contact. Imaging follow-up was performed with transcranial Doppler ultrasound (TCD) at 30 days, 6 months, 12 months, and yearly thereafter. In patients with lesions difficult to visualize with TCD, digital subtraction angiography, or computed tomography angiography in those patients who refused digital subtraction angiography, was performed between 6 and 12 months after the intervention.

Study End Points
Technical success was defined angiographically as a reduction in stenosis severity to ≤50% luminal narrowing with improvement in distal blood flow and the absence of a flow-limiting dissection or distal embolus. The 2 clinical outcomes were 30-day periprocedural occurrence of a stroke or death (although all complications were prospectively recorded) and the cumulative ipsilateral stroke rate, intracerebral hemorrhage rate, and vascular death at follow-up. Restenosis was defined angiographically as stenosis ≥50% within the treated segment. The indications for follow-up angiography included an intrasosseous location of the lesion (ie, petrous internal carotid artery), placement of a DES, a doubling of the in-segment mean flow velocities compared with the immediate postprocedure TCD mean flow velocities, or any recurrent symptoms in the territory of the treated vessel.

Statistical Analysis
Data are presented as median (interquartile range [IQR]) for continuous variables and as percentage (count) for categorical variables. We estimated the rate of different outcomes by the Kaplan-Meier method (Figure). Comparison of the restenosis rate at 1 year between baseline and angiographic characteristics was performed with log-rank tests; a Cox proportional-hazards model was used to estimate the relative risk of restenosis at 1 year. The proportional-hazards assumption was examined by log-log survival plots. Statistical testing was done with a 1-tailed α level of 0.05. Data were analyzed with Statview 5.0 software (SAS Institute Inc, Cary, NC).

Results
A total of 69 procedures in 53 patients were performed. Eleven (15.9%) of these procedures were performed in the setting of acute ischemic stroke or crescendo TIA despite antithrombotic therapy. Multiple procedures in the same patients were characterized by retreatment for restenosis (9/16), treatment of a tandem lesion (4/16), or treatment of an associated lesion in a different vascular territory (3/16). There were 40 men and 13 women with a median age of 67 years (IQR, 58.7 to 75.0 years). Presenting symptoms were ischemic strokes in 64.1% and TIAs in 35.9%. Other patient baseline characteristics are listed in the Table. The median percent stenosis was reduced from 85% (IQR, 70% to 95%) to 0% (IQR, 0% to 26%). In 53 of 69 (76.8%) procedures, a
stent was implanted (42 bare metal stents and 11 DESs; Cypher, Cordis Corp; or Taxus, Boston Scientific Inc). The technical success rate for endovascular therapy was 98.6%; in 16 of 69 (23.2%) procedures, stents were not needed or could not be delivered (after 3 attempts), and only angioplasty was performed. In 6 of 69 (8.7%) procedures, stents could not be delivered (in 1 case, a DES could not be delivered and a nitiol stent was implanted instead), and in 10 of 69 (14.5%), stenting was not necessary. Failure of stent delivery occurred for middle cerebral artery (2/6) and internal carotid artery (4/6) stenoses.

The periprocedural stroke/mortality rate was 10.1% (7/69). These complications occurred: during the procedure in 3 cases, between 7 and 24 hours in 2, and between 1 and 7 days in 2. There were 3 cases of subarachnoid hemorrhage (2 minor and 1 fatal), 3 ischemic strokes (2 of which were related to perforator occlusion after endovascular treatment of a basilar artery stenosis), and 1 intracerebral hemorrhage (hyperperfusion related). In 5 of 7 procedures in which a complication occurred, intracranial stenting was performed. Sixty-six of 69 procedures (95.7%) were performed in awake patients, and only 4.3% were performed under general anesthesia. All patients (3/53) with subarachnoid hemorrhage were treated in awake procedures.

During the median follow-up period of 24 months (IQR, 10.25 to 36.5 months), recurrent events occurred in 4 of 53 (7.5%) patients: 1 had a TIA 2 weeks after the intervention, 1 had a TIA at 6 months, 1 had a stroke at 6 months, and 1 had a TIA at 1 month and a stroke at 2 years. Restenosis was identified in 11 of 69 (15.9%) treated vessels (3 were in-stent restenoses and 8 were postangioplasty restenoses). The restenosis rate was 15.9% at 1 year, and no restenosis was identified after 1 year. The restenosis rate was 50% after angioplasty (8/16), and 7.5% (4/53) after stenting (log-rank P = 0.01; hazard ratio = 5.02; 95% CI, 1.22 to 20.68). Other factors associated with restenosis were vessel size < 2.5 mm (log-rank P = 0.001; hazard ratio = 4.78; 95% CI, 1.35 to 16.93) and interventions performed in the setting of acute stroke (log-rank P = 0.01; hazard ratio = 6.36; 95% CI, 1.78 to 22.56). No restenosis was documented after DES implantation. Two restenoses were symptomatic (18.2% of the restenotic vessels, representing 2.9% of all treated vessels) and occurred within 6 months of the intervention. In 1 case, TCD missed the restenotic lesion, and in 2 cases, TCD overcalled it compared with angiography.

The cumulative 2-year event rate (periprocedural and follow-up disabling stroke and death) was 13.0%. All-cause mortality (vascular and nonvascular) was 22.6% during the follow-up period, and myocardial infarction occurred in 9.4%.

**Discussion**

In this current series, intracranial angioplasty and stenting were associated with low 30-day complication rates and a low rate of recurrent ischemic events. Compared with the available data on the natural history of medically treated symptomatic intracranial atherosclerosis, the long-term outcomes of intracranial angioplasty and stenting in this series have a favorable profile. Recurrent strokes or deaths occurred in 13.0% of patients within a median follow-up period of 24 months, whereas the data from WASID showed 22.1% annual stroke and death rates in the subset of patients with ≥70% stenosis. All of our patients had >70% stenosis, a factor described to be associated with a greater risk of stroke. The 10.1% periprocedural complication rate observed in our series compares favorably with those presented by other groups, which are as high as 28%. However, acute ischemic stroke patients were included in this series, whereas in other studies, patients were not treated until 4 to 6 weeks after the acute event. In unstable stroke patients, Gupta et al reported a 50% periprocedural rate for major complications. Obviously, the patient population and the delay to treatment after the stroke may affect the risk of the procedure.

In this series, the overall risk of restenosis appears to be low. Restenosis occurred in 15.9% of treated segments, a rate that is below the 32% rate previously seen in a study of a balloon-expandable stent designed for the cerebral vasculature. This discrepancy might be explained in part by the use of DESs in our series, which were deployed in 20.7% of vessels. Among these restenotic vessels, 18.2% were symptomatic and required a repeat endovascular procedure, thus exposing the patients to additional periprocedural risks. Restenosis arose predominantly after angioplasty, although others have published that angioplasty alone is durable. Our results suggest otherwise, and when possible, we will deploy a stent. However, this situation (symptomatic restenosis after angioplasty) represented a low proportion of target-vessel revascularizations (2.9% in our series) and has to be balanced with the difficulties in stent delivery, which was not possible in 10% of the procedures that included coronary equipment. Although DESs have been reported to be safe and effective with minimal restenosis rates, data from the literature on coronary cases suggest that stent thrombosis with DESs may occur very late during follow-up, when many patients have discontinued their antiplatelet therapy. These findings suggest a potential concern with the widespread use of DESs in the intracranial vasculature.

Limitations of this study include the lack of angiographic follow-up in all patients. This likely resulted in an underrepresentation of the rate of restenosis, particularly in those treated with stents, because there have not been any validated means of assessing in-stent restenosis in the intracranial vasculature. TCD has been used by others to follow up patients with vertebrobasilar stents, but it has not been validated against the “gold standard” (angiography). Because we had clinical follow-up data from all patients, the rate of symptomatic restenosis seen in this series is accurate and more clinically relevant than asymptomatic restenosis.

In conclusion, this study suggests that intracranial stenting favorably reduces the rate of recurrent events in comparison with the natural history of symptomatic, severe intracranial stenoses. Restenosis after treatment seems to be more frequent after angioplasty alone and is associated with a vessel size < 2.5 mm or interventions that are performed in the setting of an acute stroke. The results of this study imply that although it may now be appropriate to carry out a randomized comparison between medical therapy and endovascular therapy, the endovascular technique of choice is yet to be defined. However, stenting appears to be superior to angioplasty alone
in restenosis and recurrent event prevention, but it is not yet clear which stent type is superior. More clinical data are needed to resolve this issue.

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References


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