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Drug-Eluting Stents for the Treatment of Intracranial Atherosclerosis

Initial Experience and Midterm Angiographic Follow-up

Alex Abou-Chebl, MD; Qasim Bashir, MD; Jay S. Yadav, MD

Background and Purpose—Intracranial stenting is associated with a 32% rate of restenosis. Drug-eluting stents (DES) have revolutionized the treatment of coronary artery disease and have greatly reduced the risk of in-stent stenosis. We present our experience with the feasibility and safety of using DES for patients with symptomatic intracranial atherosclerosis.

Methods—All of the patients had >70% stenoses and had failed maximal medical therapy. They were pretreated with aspirin, clopidogrel, and intraprocedural heparin. All of the lesions were predilated, and balloons and stents were slightly undersized. Clopidogrel and aspirin were continued for 1 year, and patients had clinical follow-up and vascular imaging at 30 days, 6 months, and 1 year.

Results—Eight patients with intracranial internal carotid artery (3), middle cerebral (2), basilar (2), and vertebral artery (1) stenoses were successfully treated with 4 Cypher (Cordis Corp) and 4 Taxus (Boston Scientific Inc) stents. The mean stenosis severity was reduced from $84.4\% \pm 10.2\%$ to $2.5\% \pm 4.6\%$. One patient had an intraprocedural retinal embolism, but there were no other complications. Over a mean follow-up of 11.1 ± 4.9 months (range, 2 to 17.3 months), patients have had repeat angiography (5) or transcranial Doppler with or without CT angiography (3). None of the patients have had clinical or significant angiographic restenosis or required target vessel revascularization.

Conclusions—Elective intracranial stenting with DES appears to be feasible and safe, but additional clinical experience is required to assess its efficacy. (*Stroke*. 2005;36:e165-e168.)

Key Words: angiography ■ intracranial arterial diseases ■ ischemia ■ stents

Stenting for the treatment of intracranial atherosclerosis is a nascent therapy with much promise. Unfortunately, the risks with such interventions remain high, and restenosis risk is $\approx 32\%$.¹ The reduction of in-stent restenosis is desirable, because restenosis is associated with a high rate of recurrent stroke, and repeat interventions reexpose patients to procedural risks.¹ Restenosis has also been a major problem with stenting of coronary arteries for coronary atherosclerosis (CAD) but has been effectively addressed by the use of drug-eluting stents (DES).^{2,3} These devices release drugs that prevent the proliferation of the cells involved in the restenotic process and have effectively reduced coronary artery restenosis to $\approx 5\%$.^{2,3} DES have been studied extensively in the treatment of CAD but to our knowledge have not been systematically studied for the treatment of intracranial atherosclerosis, except in an animal model.⁴ We have used DES to treat 8 patients with intractable cerebral ischemia attributable to intracranial atherosclerosis. In this report, we present our clinical results with angiographic follow-up.

Methods

Patient Selection and Data Collection

We reviewed our prospectively collected interventional database to identify patients who were treated with DES for symptomatic, severe (>70%) intracranial atherosclerosis. Only patients who had failed standard medical therapy with a combination of antithrombotic agents and who gave informed consent were treated. On a compassionate use basis, our Institutional Review Board has approved the use of commercially available products for the treatment of intracranial stenoses.

Periprocedural Medical Treatment

All of the patients were pretreated with 325 mg of aspirin and 75 mg of clopidogrel for ≥ 4 days before intervention. Unfractionated heparin was given to all of the patients intraprocedurally to achieve an intraprocedural activated clotting time of 250 to 300 seconds and was reversed postprocedurally. All of the procedures were performed under local anesthesia, and, throughout the intervention, brief neurological assessments were performed to assess for headache and signs of ischemia.

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TABLE 1. Clinical Characteristics (n=8)

Characteristic	N (%)
Age (y), mean (range)	65.6 (43–75)
Male	6 (75%)
Hypertension	5 (62.5%)
Diabetes Mellitus	4 (50%)
Smoking	3 (37.5%)
Hyperlipidemia	4 (50%)
Peripheral Vascular Disease	3 (37.5%)
Coronary Artery Disease	4 (50%)

Interventional Technique

All of the patients underwent thorough cerebral angiography with an emphasis on defining the following lesional and anatomical characteristics: vessel reference diameter, lesion length, eccentricity, and the presence of perforating vessels or branches within the lesion or adjacent vessel segments. Via a transfemoral approach, a 70- to 80-cm-long 7 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 (ICA) or vertebral artery (VA) at the C2 level. Interventions were performed with 0.014-inch coronary balloon and stent delivery systems over soft-tipped, hydrophilic guide wires. Wire manipulation and placement were guided by patient discomfort, if any. Angioplasty was performed with an undersized coronary balloon (Maverick, Boston Scientific Inc), which was slowly inflated to its nominal pressure. Balloon inflations were guided by patient discomfort; if pain developed, then additional balloon inflation was stopped, and a neurological assessment was performed.

Provisional 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. As with angioplasty, pain or discomfort were used to guide stent delivery and deployment. Postdilation with a balloon sized 1:1 with the treated segment was performed when needed to ensure complete stent expansion.

TABLE 2. Clinical and Technical Details

Patient	Age	Recurrent Clinical Syndrome	Cerebral Imaging Results	Vessel	Angiographic % Stenosis*	Stent Size	Stent Type	Post % Stenosis	Complications
1	55	Stroke	Cortical Borderzone Infarcts, Contralateral ICA Occlusion	ICA, Cavernous	85%	3.5×18	Cypher	0%	No
2	43	Stroke	Small Parietal Cortex Infarct, Impaired Cerebrovascular Reserve by Breath Holding TCD	MCA	95%	2.5×8	Cypher	0%	No
3	62	Stroke	Hemi-Pontine Infarct	VA	80%	3×13	Cypher	10%	No
4	73	TIA	Bilateral Cerebellar Infarcts	BA	90%	2.5×18	Cypher	0%	No†
5	73	Stroke	Frontal Cortex Infarct	ICA, Cavernous	70%	3.5×20	Taxus	0%	No
6	72	TIA	No Infarcts by DWI	ICA, Siphon	70%	3×8	Taxus	10%	No
7	72	Stroke	Deep Borderzone Infarcts, Large PWI/DWI Mismatch	MCA	90%	3×12	Taxus	0%	Yes‡
8	75	TIA	No Infarcts by DWI	BA	95%	3×8	Taxus	0%	No
Mean	65.6				84.4%			2.5%	
Std. Dev.	11.4				10.16%			4.6%	

ICA indicates internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; TIA, transient ischemic attack; TCD, transcranial Doppler; PWI, perfusion weighted imaging; DWI, diffusion-weighted imaging; Std. Dev, standard deviation. *Calculated with the following formula $(d/r) \times 100$, where d is the diameter of the lesion at its narrowest and r is the normal reference diameter just distal to the stenosis or just proximal if no normal artery distal to lesion. †Asymptomatic, nonflow-limiting dissection. ‡Retinal embolism from guide catheter.

Postprocedural Management

Postprocedure patients were sent to the neurological intensive care unit for observation and continuous arterial blood pressure monitoring to keep systolic blood pressures <140 mm Hg. Patients were discharged to home the following day on a regimen of 325 mg of aspirin lifelong and 75 mg of clopidogrel daily for 1 year. All were followed clinically and with transcranial Doppler ultrasound (TCD) at 30 days, 6 months, 1 year, and yearly thereafter. All of the patients were also asked to return for a follow-up angiogram between 6 months and 1 year after treatment.

Outcome Measures

All of the adverse events were noted prospectively. Technical success was defined angiographically as a reduction in stenosis severity to $\leq 50\%$ luminal narrowing without angiographic evidence of distal embolization, flow-limiting dissection, or contrast extravasation. Angiographic restenosis was defined as $\geq 50\%$ stenosis within the stent or just outside the stent margins.

Results

Eight patients were successfully treated, 4 with Cypher (Cordis Corp) and 4 with Taxus (Boston Scientific Inc) DES. Three ICA, 2 middle cerebral, 2 basilar (BA), and 1 vertebral artery were treated. All 8 of the patients had recurrent cerebral ischemia despite medical therapy with aspirin and clopidogrel (6) or warfarin (2). Patient clinical details are listed in Tables 1 and 2.

The mean stenosis severity was reduced from $84.4\% \pm 10.2\%$ to $2.5\% \pm 4.6\%$ (Table 2). There was 1 clinical complication not related to the stent itself (retinal embolism during guide catheter removal) and 1 poststenting complication (nonflow-limiting, asymptomatic BA dissection). During the mean follow-up period of 11.1 ± 4.9 months, there have been no recurrent cerebral ischemic events, and all of the patients remain neurologically independent.

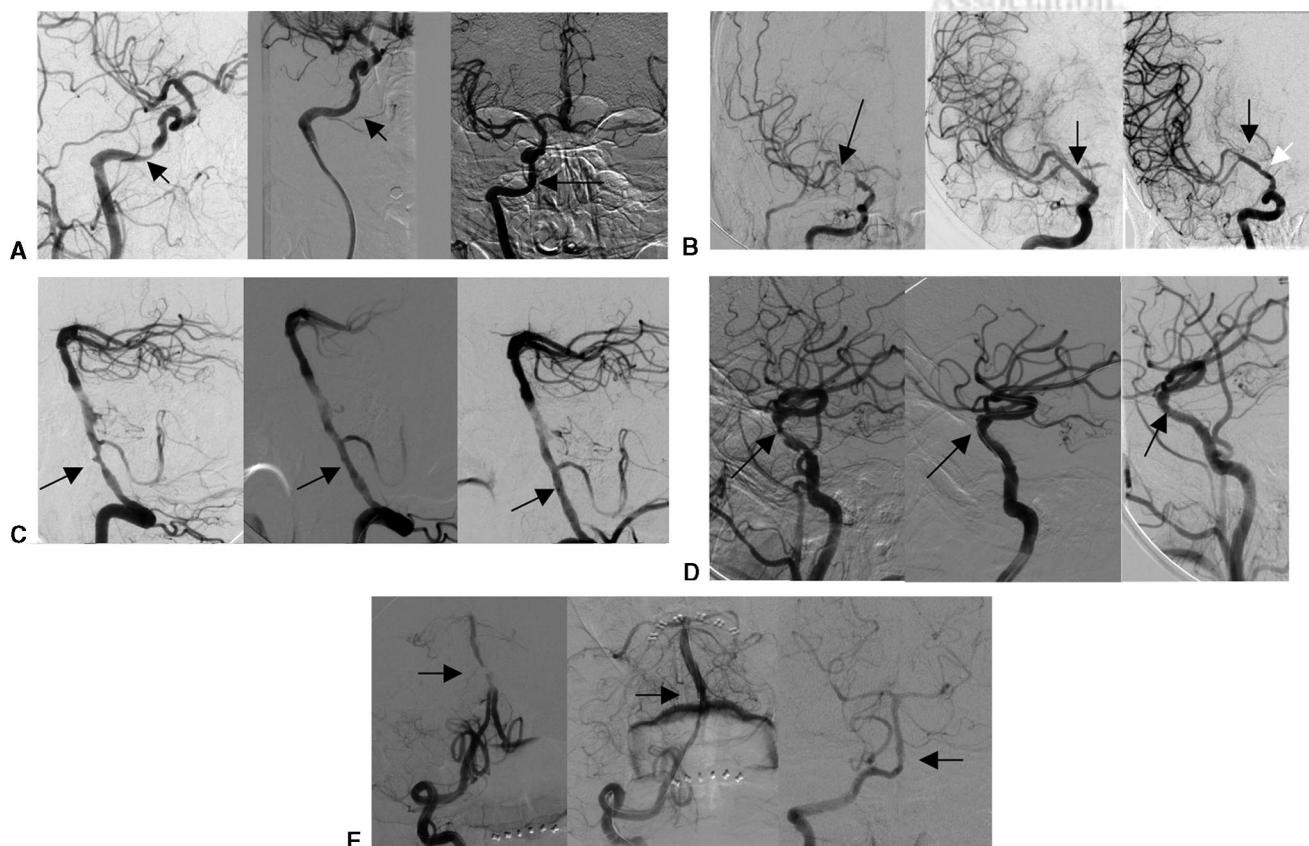
TABLE 3. Follow-up Details

Patient	Duration of Clinical Follow-up, Months	Clinical Outcomes	Time to Follow-up Imaging, Months	Follow-up Angiography Findings, % Stenosis	TCD MFV, Initial/Latest Follow-up, cm/s*
1	17.3	No Recurrent Events	15.2	0	†/108
2	14.7	No Recurrent Events	12.6	29%	258/130
3	14.7	No Recurrent Events	12.6	0	†/60
4	2	No Recurrent Events	2	‡	170/50
5	12.9	No Recurrent Events	10.8	0	†/38
6	10.6	No Recurrent Events	10.4	‡	†/40§
7	9.6	No Recurrent Events	7.5	‡	†/68¶
8	7.6	No Recurrent Events	5.5	0	†/88
Mean	11.1		9.6		
Std. Dev.	4.9		4.3		

TCD indicates transcranial Doppler ultrasound; MFV, mean-flow velocities; Std. Dev, standard deviation. *All follow-up TCD's performed same day as angiogram or within 1 week of angiogram; †Preprocedure TCD not done; ‡Patient refused angiography or too early for angiographic follow-up; §Internal carotid pulsatility index of 1.2 (contralateral 1.1) and normal MFV proximal and distal to stent suggest no hemodynamically significant in-stent stenosis; ¶Middle cerebral artery MFV are in normal range and good opacification distal to stent by computed tomography angiography suggest no significant in-stent stenosis.

Follow-up cerebral angiography has been obtained in 5 of 8 patients at a mean of 9.6 ± 4.3 months (range, 2 to 15.2) after stenting (Table 3). There was no evidence of aneurysm formation or other arterial abnormality by angiography (Figure). Two patients have refused additional angiography but have returned for follow-up with TCD, combined with CT

angiography in 1 patient. In both cases, there was a normal flow pattern proximal to and distal to the stent, and in the patient with the middle cerebral stent, the in-stent mean flow velocities were normal, suggesting that there was no significant stenosis. One patient has not reached the 6-month angiographic follow-up point, but on TCD at 2 months, the



Angiographic images of the 5 patients for whom a follow-up angiograms were obtained. Each series (A–E) contains (left to right) the initial pretreatment angiogram, the immediate poststenting angiogram, and the most recent angiographic follow-up image. In each image, the arrow points to the stented segment. Note in B the 1 year follow-up image shows a mild degree of neointimal growth indicated by the white arrow.

BA stent was widely patent. None of the patients have had significant angiographic or clinical restenosis or required target vessel revascularization. The asymptomatic BA dissection complicating a Taxus (Boston Scientific Inc) DES was completely healed on the 6-month angiogram (Figure 1).

Discussion

To our knowledge, this is the first report of the use of DES in the intracranial vasculature with angiographic and clinical follow-up. In this series, the use of DES was feasible and safe, because there were no untoward effects associated with the stents. The midterm safety of these devices appears to be favorable with no evidence of arterial toxicity. Importantly, there have been no delayed recurrent ischemic events or cases of stent thrombosis over a mean of 11.1 months of follow-up.

The use of DES in the intracranial vasculature is desirable because of the high restenosis risk ($\approx 32\%$) associated with bare metal stents (BMS).¹ In the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial of a BMS developed for intracranial stenoses, restenosis was associated with a 39% rate of recurrent symptoms.¹ Drug-eluting stents have revolutionized the treatment of CAD by reducing the risk of in-stent stenosis from 30% to $\approx 5\%$, and they should have a similar effect on intracranial atherosclerotic lesions.^{2,3} The ultimate goal of stenting is to maintain adequate cerebral perfusion over the lifetime of the patient; by preventing restenosis with DES, patients may be spared the risk of recurrent ischemia, as well as the risks associated with intracranial interventions, which may be between 10% and 30%.^{5,6}

The histological structure of the intracranial arteries differs from that of the coronary arteries, and, as a consequence, there are theoretical risks (eg, vessel toxicity and delayed endothelialization) associated with DES that are not associated with BMS. Vessel toxicity occurs by a direct effect of the drugs. The safety of DES in the intracranial vasculature was studied in a model using Cypher (Cordis Corp) stents in the BA artery of dogs.⁴ This study found no evidence of arterial or brain tissue toxicity and concluded that these devices were safe within the intracranial vasculature. The total dose of drug released to tissues by DES is very small compared with the known toxic doses of both sirolimus and paclitaxel, and tissue toxicity does not appear to be an issue.^{2,3} Arterial toxicity was assessed in the current series by angiography, and no evidence (eg, aneurysm) of it was found. Cerebral toxicity was assessed by clinical status, which was stable in all of the patients.

The other major concern with DES is delayed endothelialization, which may be significantly delayed and can result in stent thromboses even 6 to 12 months after implantation.⁷ Stent thrombosis may also occur with BMS and is, therefore,

not exclusive to DES.⁷ This phenomenon is rare and may be prevented by the prolonged (for ≥ 1 year) use of dual antiplatelet therapy,⁷ which is the reason that the patients in this series were treated with combination therapy for 1 year. This is potentially risky, because the prolonged, combined use of aspirin and clopidogrel has recently been found to be associated with an increased risk of intracerebral hemorrhage in a stroke population with a high prevalence of small vessel disease and diabetes.⁸ The risk of intracerebral hemorrhage with the dual therapy in other populations, particularly those with large artery stenosis or those who have intracranial stents, is unknown and warrants additional study, particularly in patients with intracranial DES.⁹ The limitations of this study include the small number of patients and the lack of angiographic follow-up in some of the patients, because the intracranial ICA cannot be insonated fully with TCD and CT angiography.

In summary, in this series, we found that the use of DES was feasible and safe for the treatment of intracranial atherosclerosis. Larger, longer-term studies are needed, but DES are a promising new therapy for this potentially devastating disease.

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