Safety, Feasibility, and Short-Term Follow-Up of Drug-Eluting Stent Placement in the Intracranial and Extracranial Circulation

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Background and Purpose—The use of bare metal stents to treat symptomatic intracranial stenosis may be associated with significant restenosis rates. The advent of drug-eluting stents (DESs) in the coronary circulation has resulted in a reduction of restenosis rates. We report our technical success rate and short-term restenosis rates after stenting with DESs in the intracranial and extracranial circulation.

Methods—This study was a retrospective review of the period between April 1, 2004, and April 15, 2006, of 59 patients with 62 symptomatic intracranial or extracranial atherosclerotic lesions at 2 medical centers (University of Pittsburgh and Borgess Medical Center).

Results—The mean age of our cohort was 61 ± 12 years. The location of the 62 lesions was as follows: extracranial vertebral artery 31 (50%), intracranial vertebral artery or basilar artery 18 (29%), extracranial internal carotid artery (ICA) near the petrous bone 5 (8%), and intracranial ICA 8 (13%). There were 2 (3%) periprocedural complications: 1 non—flow-limiting dissection and 1 disabling stroke. Fifty vessels were available for follow-up angiography or computed tomography angiography at a median time of 4.0 ± 2 months. A total of 2 of 36 extracranial stents (7%) and 1 of 26 intracranial stents (5%) were found to have restenosis ≥50% at follow-up.

Conclusions—This report demonstrates that DES delivery in the intracranial and extracranial circulation is technically feasible. A small percentage of patients developed short-term in-stent restenosis. Longer-term follow-up is required in the setting of a prospective study to determine the late restenosis rates for DESs in comparison with bare metal stents. (Stroke. 2006;37:2562-2566.)

Key Words: angioplasty ■ intracranial stenosis ■ stenting ■ stents

Intracranial atherosclerosis accounts for roughly 10% of ischemic strokes in the United States each year.1 A recent multicenter, randomized, controlled study has shown that patients with symptomatic intracranial disease treated with aspirin did not have a higher risk of recurrent stroke when compared with patients taking Coumadin.2 With best medical therapy, the rate of stroke ipsilateral to the stenosis is 11% in the first year, but it is nearly 2 times higher if the stenosis is ≥70%.3

Failure of medical therapy to reduce the rate of stroke has led to advances in endovascular options for symptomatic intracranial atherosclerosis. Coronary stents4 or primary angioplasty5 have been used to improve the luminal diameter of the vessel. More recently, a self-expanding stent with improved navigability has been approved under the US Food and Drug Administration Humanitarian Device Exemption.6 A major concern for using bare metal stents for symptomatic intracranial and extracranial stenting has been the rate of restenosis, reported to be as high as 32%.4 The recent advent of drug-eluting stents (DESs) in the coronary circulation has significantly reduced rates of restenosis, from roughly 30% to 4% to 8% at 9-month follow-up.7,8

We sought to determine the safety, technical feasibility, and short-term restenosis rates for DESs in the extracranial and intracranial cerebral circulation in patients with a symptomatic atherosclerotic lesion.

Patients and Methods
This is a retrospective study of all patients from April 1, 2004, to April 15, 2006, at 2 medical centers (University of Pittsburgh Medical Center, Pittsburgh, Pa, and Borgess Medical Center, Kalamazoo, Mich) who underwent attempted stenting and angioplasty of an extracranial vertebral artery lesion, extracranial carotid...
TABLE 1. Demographic Information for the Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD), y</td>
<td>61 ± 12</td>
</tr>
<tr>
<td>Men</td>
<td>48 (83)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (86)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (40)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39 (67)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>18 (31)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>35 (60)</td>
</tr>
</tbody>
</table>

Each patient experienced stroke or transient ischemic attack (TIA) referable to the stenotic vessel, with the likely mechanism being artery-to-artery embolism or hemodynamic compromise to the affected territory. Revascularization was considered only in patients who developed symptoms of stroke or TIA, despite being on maximal medical therapy, defined as an antiplatelet agent or warfarin. This retrospective review was performed after permission from the institutional review boards at both institutions. Clinical, demographic, and angiographic data were acquired through investigation of the patient’s medical charts and angiograms.

All patients were given aspirin and a loading dose of clopidogrel of 300 mg the night before the procedure if they were not already taking these medications. All patients were prescribed aspirin 81 mg/d or 325 mg/d and clopidogrel 75 mg/d after the procedure for at least 3 months at the University of Pittsburgh and at least 6 months at Borgess Medical Center. Aspirin was continued indefinitely after cessation of clopidogrel. Conscious sedation was used for all extracranial stenting procedures, General anesthesia was used in 21 patients undergoing intracranial stenting procedures, whereas conscious sedation was used in 5 patients undergoing intracranial stenting in the anterior circulation. All patients in this cohort were considered for stenting with a DES as first-line therapy. In instances where a DES could not be delivered, a bare metal stent was attempted.

A 5F diagnostic catheter was placed proximal to the stenotic segment and exchanged for a 6F or 7F guiding catheter. At this point, patients were given intravenous heparin to maintain an activated clotting time between 200 and 300. The lesion was traversed with a 0.014-inch microwire. Taxus (Boston Scientific, Inc) or Cypher (Cordis Corp) balloon-mounted stents were delivered over the 0.014-inch microwire. The diameter of the stent deployed was determined by undersizing it by 10% of the lumen diameter. The shortest length for the stent was used to completely cover the atheromatous segment. The stent diameters ranged from 2.5 to 3.5 mm, whereas the length ranged from 8 to 18 mm. All treated lesions were <16 mm long. Each stent was deployed with slow inflation of the balloon over 30 to 45 seconds under fluoroscopic guidance to ensure that the stent did not displace forward across the lesion. Poststent deployment control runs were performed to measure the diameter of the vessel after stenting. Heparin was not reversed after the procedure, and all patients were admitted to a neurological step-down unit when an extracranial stent was placed or to an intensive care unit when an intracranial stent was placed.

Follow-up conventional angiograms (n=41) or computed tomography (CT) angiograms (n=7) were available for 48 patients with 50 stents at 3 months or later. Eleven patients with 12 stents did not have follow-up studies owing to recent stent placement with follow-up not scheduled until a later time, patient refusal, or loss to follow-up. These follow-up studies were investigated for restenosis that was defined as a luminal narrowing of ≥50% in the target vessel. Clinical follow-up was available for these same 48 patients. Any new neurological event that patients might have experienced after the procedure was extracted from their clinical follow-up in the medical records.

TABLE 2. Summary of Stent Delivery Success, Complications, and Restenosis by Lesion Location

<table>
<thead>
<tr>
<th>Location of Stent</th>
<th>No. of Attempted Stents Placed</th>
<th>Stent Delivery Success, n (%)</th>
<th>Periprocedural Complications, n (%)</th>
<th>Stents Followed Up, n</th>
<th>No. Restenoses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial vertebral artery</td>
<td>31</td>
<td>31 (100)</td>
<td>0 (0)</td>
<td>27</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Intracranial vertebral artery/basilar artery</td>
<td>19</td>
<td>18 (95)</td>
<td>1 (6)</td>
<td>14</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intracranial ICA</td>
<td>10</td>
<td>8 (80)</td>
<td>1 (13)</td>
<td>6</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Extracranial ICA</td>
<td>5</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Any intracranial vessel</td>
<td>29</td>
<td>26 (90)</td>
<td>3 (12)</td>
<td>20</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Any extracranial vessel</td>
<td>36</td>
<td>36 (100)</td>
<td>0 (0)</td>
<td>30</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

A total of 59 patients underwent stenting of 62 vessels. The mean age for the cohort was 61±12 years, with 42 patients (71%) found to have an infarct confirmed on magnetic resonance imaging or CT at the time of admission. Seventeen (29%) patients presented with TIA referable to the vessel and who underwent stenting. Table 1 summarizes the demographic information for this cohort. The location of stent placement was as follows: extracranial vertebral artery 31 (50%), intracranial vertebral artery or basilar artery 18 (29%), extracranial internal carotid artery (ICA) near the petrous bone 5 (8%), and intracranial ICA 8 (13%). A Cypher stent was placed across 16 lesions (26%), whereas a Taxus stent was placed across 46 lesions (74%). Fifty-six of the 62 (90%) lesions treated had a stenosis ≥70%.

The success rate for delivery of a DES was 62 of 65 vessels (95%). The location of the 3 vessels with failed delivery of a DES was 2 intracranial ICAs and 1 intracranial vertebral artery; thus, the failure rate for delivery of an intracranial stent was 10% (3 of 29; Table 2). A bare metal stent was eventually successfully delivered to the intracranial vertebral artery lesion, but no stents were successfully navigated to the 2 intracranial ICA lesions. The mean stenosis before treatment was 83±12%, with a reduction of stenosis to 12±11% after the procedure in patients with successful stent delivery. Successful reduction of the stenosis to <50% occurred in 61 of 62 vessels (98%). The patient with unsuccessful reduction of the stenosis to <50% had a heavily calcified intracranial carotid lesion (the Figure). During inflation of the balloon to deploy the stent, it was noted that the balloon did not fully expand, likely because of the underlying calcified plaque. The patient returned 4 months later with an acute stroke secondary to an occluded stent and was subsequently severely disabled as a result of the stroke. There were 2 periprocedural complications: 1 non–flow-limiting dissection.
A 63-year-old woman presented with left hemiparesis and was found to have scattered infarcts on diffusion-weighted imaging in the right hemisphere. The patient was referred for stenting of an intracranial ICA stenosis noted on magnetic resonance angiography (not shown). A, Lateral view shows a 60% calcified right ICA lacerum segment stenosis (solid black arrow). B, “Road map” image reveals crossing of a Taxus stent of the stenotic segment (dotted black arrow). C, After stent placement, the calcified region of the stenosis did not dilate, and the patient was left with a 60% stenosis of the segment (solid black arrow). D, The patient returned 4 months later with a National Institutes of Health Stroke Scale score of 16. She was found have a right carotid occlusion on angiography (solid black arrow). E, Selective right ICA injection shows extensive thrombus across the stent, along with deformation of the stent (black arrowheads) across the calcified lesion. Intracerebral tissue plasminogen activator was infused and balloon angioplasty was attempted without success. The patient developed a large infarct in the right middle cerebral artery territory and was significantly disabled as a result.

Discussion
Our report demonstrates that DESs can be successfully placed in appropriately selected patients with intracranial and extracranial atherosclerotic lesions. The patients in this cohort were selected on the basis of the absence of excessive vascular tortuosity as assessed by the operators at both institutions. The 95% rate of delivery found in our experience does not reflect the deliverability of DESs in all patients with intracranial and extracranial atherosclerotic disease owing to the selection bias. In such cases, a different technique with balloon angioplasty or other modality may have been performed. We also found that the restenosis rate at a median follow-up of 4 months was 6% for the entire cohort.

There is limited experience as to the likelihood of developing DES toxicity to the cerebral arteries in humans because of short-term follow-up. A study on the placement of sirolimus-eluting stents in canine cerebral arteries did not reveal histological evidence of toxicity. This represents the largest experience to date with the use of DESs for these arteries. The compounds used on these stents, sirolimus and paclitaxel, have been shown to reduce the response of neointimal hyperplasia by blocking mitogen-induced smooth muscle proliferation. The literature on coronary stent placement has shown that these stents significantly reduce restenosis rates, thus reducing the need for revascularization. Longer-term follow-up at 2 years shows that the biological effects of the drug polymer persist toward suppressing neointimal hyperplasia.

Patients with symptomatic intracranial atherosclerotic disease had a 1-year risk of stroke in the ipsilateral territory of 11%. This risk nearly doubles to 19% in the first year if the target vessel has a stenosis ≥70%. In our series, 90% of patients had a stenosis ≥70% and were judged to be at high risk of a subsequent stroke if maintained on medical therapy. Prior studies had suggested that posterior circulation atherosclerosis was associated with a higher risk of stroke, but a recently published prospective study did not note differences in stroke rates by location. The natural history of symptomatic cervical and ostial vertebral artery stenosis is unknown. Patients with symptomatic internal carotid artery disease at the common carotid artery bifurcation have a 13% risk of a recurrent stroke at 1 year with medical therapy, which is similar to what was recently reported in symptomatic intracranial disease. Patients who underwent stenting procedures for extracranial vertebral artery disease in this series were considered only if they had bilateral vertebral artery disease or if 1 vertebral artery was occluded with poor contribution from the posterior communicating arteries. Although the natural history of symptomatic extracranial vertebral artery...
disease is unknown, we thought that these patients were at high risk of recurrent stroke even in placed on maximal medical therapy.

Other authors have used coronary stents to treat patients with symptoms as a result of extracranial vertebral artery stenosis and intracranial lesions. The main concern related to treating extracranial vertebral artery stenosis with stents has been the rate of restenosis, ranging from 10% to 40% in the literature, whereas periprocedural complication rates and vascular tortuosity have limited the wide use of intracranial stenting. Our report demonstrates that the restenosis rate was 6% at a median follow-up of 4 months in this cohort and 7% in patients treated for extracranial vertebral artery disease. Additionally, the periprocedural complication rates were relatively low at 3%, with 1 patient developing a disabling stroke after the procedure and 1 asymptomatic dissection. The WingSpan stent system (Boston Scientific) was studied as a treatment option for patients with symptomatic intracranial atherosclerosis. This study found that the stent could be delivered successfully in 44 of 45 patients (98%). The 6-month restenosis rate was found to be 7.5% with a 30-day ipsilateral stroke or death rate of 4.5%. The SSYLVIA trial considered stent placement in the intracranial or extracranial cerebrovasculature, and the 6-month restenosis rate was 32% overall and the periprocedural complication rate was 6.6%. Our results cannot be directly compared with either of these studies because of the shorter follow-up and the retrospective nature of the study, but it does provide short-term data.

Although there is justified enthusiasm for the use of DESs because of their lower restenosis rates, caution must be used, as delayed endothelialization may occur. It is unclear whether delaying the healing process results in reductions in longer-term rates of restenosis. In addition, although reports of arterial toxicity have not been noted in the intracranial and extracranial circulation, there have been reports of delayed hypersensitivity to the stents, causing thrombosis in the coronary circulation. As experience grows with the use of DESs in the intracranial and extracranial circulation, longer-term follow-up data will become available to answer these questions.

Another caution is the placement of a stent across a calcified lesion. In coronary vessels, rates of restenosis are significantly linked to plaque burden. Calcified lesions do not allow a stent to fully expand, and thus, it leaves a small lumen with a higher chance of causing restenosis. The patient whom we describe in the Figure unfortunately developed a subacute thrombosis at 4 months, and this event may be linked to poor stent expansion in the setting of high plaque burden from a calcified lesion. We have changed our practice since encountering this patient by attempting to predilate calcified lesions first. If the lesion does not reduce to <50%, then stent placement is not attempted.

There are limitations to this study because of its retrospective nature. The first is that longer-term follow-up is necessary to determine the restenosis rates for DESs. The second is that the rate of restenosis for bare metal stents in the cerebral circulation is not well established, and as such, a randomized, controlled study would be necessary to distinguish the differences in restenosis rates between bare metal stents and DESs. The third is that we did not attempt to place these stents in locations where it was deemed that excessive tortuosity would preclude successful delivery of the stent. This caveat introduced selection bias in our cohort, but nonetheless, the results shows that these stents can be delivered and successfully deployed in select patients with a high degree of success. The fourth limitation is that 7 patients were followed up with CT angiography, which has not been validated against catheter angiography. Others have noted that CT angiography generally overestimates restenosis, and thus, it is unlikely that we underestimated the rates of restenosis in this study. Despite these limitations, this report shows that delivery of a DES to the extracranial and intracranial vessels is feasible with a high technical success rate and low complication rate. The rates of restenosis at short-term follow-up in this report are encouraging but require further investigation with longer-term follow-up.

Disclosures

None.

References


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