Sirolimus-eluting stents in the canine cerebral vasculature: a prospective, randomized, blinded assessment of safety and vessel response


Departments of Neurosurgery and Cardiology and Toshiba Stroke Research Center, University at Buffalo, State University of New York, Buffalo, New York; and The Biomedical Research Foundation of South Texas, Incorporated, San Antonio, Texas

Object. Use of the sirolimus-eluting stent has led to a reduction of in-stent stenosis following treatment of coronary atherosclerosis, whereas treatment of intracranial atherosclerosis with bare-metal stents results in excessive restenosis rates of approximately 40%. Neurotoxicity effects and vessel injury are unknown in the cerebral vasculature. To assess the safety profile and vascular effects of sirolimus-coated stents, the authors conducted a prospective comparative study in which drug-eluting and bare-metal stents were implanted in the canine basilar artery (BA).

Methods. Sixteen mongrel dogs were randomized (eight animals per group) to receive either bare-metal 1.5 × 8-mm (six-cell) stents or sirolimus-eluting stents of the same dimensions. Interventionists, histopathologists, and histopathology technicians who participated in the study were blinded to the stent characteristics. Stents were implanted in the canine BA. Serial peripheral blood samples were obtained during the 1st week after implantation to determine the time-dependent serum concentration of sirolimus. Follow-up angiographic studies were performed 30 days after stent implantation to assess the effects of stent placement on the BA and brainstem perforating vessels. Explantation of the stent and BA was performed immediately after angiography by using a pressurized formalin fixation procedure. Histological and computer-assisted morphometric analyses of specimens obtained in each animal were performed.

Sirolimus could not be detected in peripheral blood samples obtained later than 24 hours posttreatment. On follow-up angiography, all perforating vessels observed on initial angiograms remained patent, and no evidence of parent vessel damage or pseudoaneurysm formation was observed. Explanted vessels and brainstem sections did not demonstrate evidence of histological neurotoxicity, such as gliosis or infarction. No significant differences were found in the time to endothelialization of bare-metal and sirolimus-coated stents. Smooth-muscle cell (SMC) proliferation, the putative agent for restenosis, was lower in animals receiving sirolimus-coated stents (p = 0.003). Additionally, intimal fibrin density was increased in the dogs treated with sirolimus-coated stents (p < 0.0001). Histological evidence of an inflammatory response demonstrated a trend toward a reduced response in the sirolimus group (mean 0.58) compared with the bare-metal group (mean 0.83, p = 0.33).

Conclusions. No neurotoxic effects were observed in the intracranial vessel walls or brainstem tissue in which sirolimus-coated stents were implanted. Compared with bare-metal stents, the sirolimus-coated devices did not impair endothelialization and, furthermore, tended to reduce the proliferation of SMCs. These findings indicate that sirolimus-coated devices may inhibit in-stent stenosis. Further studies with longer-term follow up are required to assess the restenosis rates of sirolimus-coated stents implanted in the intracranial vasculature.

Key Words • basilar artery • sirolimus-eluting stent • dog

The recent advances in both self-expanding and balloon-mounted stents have provided clinicians with alternative treatments for symptomatic cerebrovascular atherosclerotic disease. It is estimated that 800,000 strokes occur annually in the US, of which 10% may be due to intracranial atherosclerosis. In current trials such as the Warfarin-Aspirin Symptomatic Intracranial Disease study, investigators have demonstrated a reduction in stroke risk among patients receiving antithrombotic therapy compared with those receiving aspirin alone. Interestingly, this reduction was not noted in the region corresponding to the stenotic vascular territory. Moreover, approximately half of the patients with 50% or more intracranial stenosis will experience recurrent ischemic symptoms, despite optimal antithrombotic therapy.

Although medical management is likely indicated for patients with moderate intracranial stenosis, the optimal treatment regimen for symptomatic patients with high-grade disease remains unclear. What is of most concern is that recurrent symptoms often result in death or significant neurological morbidity. Several clinical investigators have examined the role of surgical bypass or stent placement for intracranial atherosclerosis. In patients experiencing ischemic symptoms, surgical bypass procedures may help prevent ischemia recurrence or stroke. Nevertheless, these pro-
Sirolimus-eluting stents in the canine cerebral vasculature

Cedures will not ameliorate ischemic symptoms resulting from embolic debris. Furthermore, although low morbidity rates have been reported for posterior circulation bypasses involving the posterior inferior cerebellar artery, 10% or higher mortality rates have been reported for those involving the posterior cerebral and superior cerebellar arteries.5–25 These results compare favorably with the 30% mortality rate reported initially for posterior circulation stent placement.16 In more recent reports, no or low rates of permanent neurological morbidity have been associated with the use of conventional and staged stent procedures.10,16,17,22,24

Perhaps the most significant concern regarding intracranial stent placement is the long-term effect of stent implantation on cerebral vessels. Because cerebral vessels contain a greater relative percentage of SMCs than peripheral vessels,14 concerns exist regarding the propensity for in-stent stenosis and long-term symptom recurrence. As demonstrated in the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial,26 more than 40% restenosis was noted after stent treatment of stenoses originating intracranially and in the vertebral artery. At 6 months, more than 50% stenosis occurred in 30% of the intracranial arteries treated; the recurrent lesions produced symptoms in nearly 40% of the patients.

If the long-term benefits of intracranial stent placement are to be realized, implantable devices must be capable of deterring recurrent stenosis. Stents coated with sirolimus have been shown to reduce binary coronary artery stenosis (<50% stenosis) from 26 to 0% at 6 months.23 Sirolimus (Rapamune [generic rapamycin]; Wyeth Research, Radnor, PA) is a 31-member macrolide antibiotic with potent anti-migratory, antiproliferative, and antiinflammatory properties. At the cellular level, sirolimus has the ability to inhibit the costimulatory pathways necessary for cytokine synthesis and the DNA transcriptional processes involved in the mediation of cell cycle progression after cytokine stimulation.11,12 Sirolimus arrests cell cycle progression at the G/S transition in numerous cell types, including vascular SMCs and T lymphocytes.24 The antiproliferative and antimigratory actions of sirolimus on vascular SMCs are mediated by binding to its intracellular receptor (FKBP12). This complex then inhibits a kinase called the target of rapamycin, which is involved in the pathway that controls cell cycle progression in vascular SMCs through the regulation of phosphorylation of cyclin-dependent kinase, retinoblastoma protein p70S6k, and eukaryotic translation initiation factor 4E–binding protein.

Questions regarding potential neurotoxicity and intracranial vessel injury have precluded the intracranial use of stents coated with sirolimus. To assess the safety and side effects of sirolimus-coated stents implanted in intracranial vessels, we conducted a prospective study in which well-defined end points were used to evaluate toxicity to the vasculature and surrounding tissue, as well as to confirm previous reports regarding time-dependent sirolimus levels in the blood. Using the canine BA stent model, we implanted (in a randomized and blinded fashion) bare-metal and sirolimus-eluting metal stents to assess the aforementioned parameters.

Materials and Methods

This study was approved by the University at Buffalo Animal Care and Use Committee in accordance with guidelines established by the Animal Welfare Act.6

Animal Preparation

Sixteen mongrel dogs (each weighing at least 25 kg) were randomized (eight per group) to receive either bare-metal 1.5 × 8-mm (six-cell) stents or sirolimus-eluting stents of the same dimensions. The animals were quarantined for 1 week before stent implantation to exclude from the study any dog found to have an infection or to exhibit aggressive behavior. After a general anesthetic agent had been delivered endotracheally with intubation, a 2- to 3-cm cut-down procedure was performed to expose the femoral artery and to allow primary closure of the arteriotomy after stent placement. Stents were chosen in a predetermined fashion that was not disclosed to the study interventionists, histopathologists, and histology technicians, all of whom were blinded to the stent characteristics. The devices were implanted in the canine BA across the posterior inferior cerebellar and/or labyrinthine arteries. The method of stent delivery into the canine BA has been described previously by our group.10 The stents used in this study were bare-metal or sirolimus-eluting BX Velocity stents (Cordis Corp., Miami Lakes, FL) mounted on 1.5 × 10-mm balloons. Each drug-eluting stent contained 71 μg of sirolimus.

Each dog received 3000 U heparin during the procedure and was maintained on aspirin (180 mg/day initiated 3 days before the stents were implanted) throughout the 30-day follow-up period. The animals were observed daily by staff at the research center for evidence of feeding or behavioral disorders.

Sirolimus Elution Profile

Blood samples were obtained from peripheral veins throughout the 1st week after stent implantation to determine the sirolimus elution profile. The samples were obtained at 5 and 30 minutes; at 1, 6, 9, and 24 hours; and at 3, 5, and 7 days (extracts of whole blood were analyzed). Sirolimus and the internal standard 32-desmethoxy-7,9,11,13-tetrahydro-6R-8,10,12-faumomax-yrapamycin were extracted from 0.25 ml of whole blood with sodium ethylselenediaminetetraacetic acid anticoagulant into 1-chorobutane by using a liquid–liquid extraction procedure. Chromatography of the extracts was then performed under reverse-phase conditions on a Keystone BetaBasic C4 column (Thermo Hypersil; Keystone, Bellefonte, PA) by using methanol and water containing ammonium acetate and acetic acid as the mobile-phase solvents. The compounds were detected and quantified by tandem mass spectrometry in which atmospheric pressure chemical ionization was used.

Thirty days after stent implantation, general anesthesia with endotracheal intubation was induced in the dogs and conventional angiography was performed to assess the effects of the stents on the BA and brainstem perforating vessels.

Stent Explantation

Immediately after angiography, explantation was performed using a pressurized formalin fixation procedure (Fig. 1), as follows. The animals were transported to the necropsy area while endotracheal intubation was maintained. An intercostal incision was performed, and the left sixth intercostal space was exposed, incised, and retracted. The pericardium was incised, and the descending aorta was clamped. The heart was then isolated, and a cannula was inserted to facilitate the infusion and circulation of approximately 5 L 10% formalin. After formalin fixation was completed, a craniotomy and C-1 laminectomy were performed with en bloc removal of the brain and rostral cervical spinal cord. After careful microdissection of the posterior circulation and circle of Willis, the BA and brainstem perforating vessels were removed from the brainstem and prepared for histological and computer-assisted histomorphometric analyses.

Stent Sectioning

On gross inspection of the brain a single stent was seen in the BA, which had no evidence of dissection, aneurysm, or subarachnoid hemorrhage. Multiple sections cut through the brainstem, cerebrum, and cerebellum revealed no gross abnormalities. Eight large sections from each of the brain samples were submitted for paraffin embedding and Luxol fast blue staining in cassettes labeled as follows: 1)
microscope. They were scored for their technical sectioning qual-
al before they were mounted in immersion oil for viewing under the
ctions were polished and stained with metachromatic contrast materi-
then embedded in methyl methacrylate plastic blocks, and the blocks
were slightly expanded with no breaks in their struts. The stents were
intimal SMC infiltration, and adventitial fibrosis.

objective lens for various histological changes, including mural inju-
diately after application of the pressurized formalin fixation pro-

specimens were dehydrated in a graded ethanol series and
and distal end segments, were measured and inspected under a
stent, plus one from each of the adjacent nonstent-treated proximal
branches and technical suitability for measurement.

Specimen Preparation

The specimens were dehydrated in a graded ethanol series and
embedded in methyl methacrylate plastic (Sigma Chemical Co., St.
Louis, MO). Thin cross-sections of the brainstems were made and
stained with Luxol fast blue; these sections were examined for ar-
eas of necrosis and gliosis. Using an Isomet saw (Buehler Ltd., Ev-
anston, IL), serial plastic sections were obtained from the proxi-
mal to the distal end of the BA. All sections were polished, stained
with metachromatic contrast material, and inspected for perforating
branches and technical suitability for measurement.

Three BA cross-sections sampled from along the length of the
stent, plus one from each of the adjacent nonstent-treated proximal
and distal end segments, were measured and inspected under a × 4
objective lens for various histological changes, including mural inju-
y, inflammation, endothelialization, vascularization, intimal fibrin,
intimal smooth muscle, adventitial fibrosis, and endothelial-
ization. Patency of the lumen of the pontine perforating arteries was
also evaluated.

Scoring of the Specimens

Scoring of the arterial cross-sections was performed sequentially
from the proximal to the distal end of the specimen.

Inflammation Score. An inflammation score was assigned that
was based on the presence of any significant inflammation surrounding
the stent struts, as follows: 1, involvement of less than 25% of the ar-
tery; 2, more than 25% but less than 50% of the artery; and 3, more
than 50% of the artery.

Intimal SMC Content. This feature was scored according to the fol-
lowing scheme: 1, sparse SMC density that involved any portion of
the artery or moderate SMC infiltration less than the full thickness
of the neointima that involved less than 25% of the circumference of
the artery; 2, moderate infiltration less than the full thickness of the
neointima that involved more than 25% of the circumference of the
artery or dense SMC content over the full thickness of the neointima
that involved less than 25% of the circumference of the artery; and
3, dense SMC content over the full thickness of the neointima that
involved greater than 25% of the circumference of the artery. 26
The percentage of occlusion was calculated according to the following
formula: 1 − lumen area/stent area × 100.

Intimal Fibrin Content. This feature was scored according to the
scheme just described for SMC content, but this scheme was based
on fibrin deposition density as opposed to SMC infiltration.

Endothelialization. This was defined as the extent of the circum-
ference of the arterial lumen that was covered by endothelial cells
and was scored according to the following scheme: 1, less than 25%;
2, 26 to 74%; and 3, 75% or more. 26

Histological sections of the artery were also examined for endo-
thelialization, significant intimal hemorrhage, fibrinoid median ne-
crosis, medial fibrosis, the nature of the inflammatory cell infiltrates,
and the presence of multinucleated giant cells. Separation of any
coating additive with an inflammatory reaction was also noted. Dis-
section of the artery or perforating vessel with hemorrhage as well as
any occlusion of the side branches were likewise recorded.

Statistical Analysis

As noted earlier in this paper, the various histological and mor-

<table>
<thead>
<tr>
<th>Timing of Blood Sample</th>
<th>Dog No.</th>
<th>Serum sirolimus concentrations (ng/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5 mins</td>
<td>0.29</td>
<td>NA</td>
</tr>
<tr>
<td>30 mins</td>
<td>0</td>
<td>0.286</td>
</tr>
<tr>
<td>1 hr</td>
<td>0</td>
<td>0.277</td>
</tr>
<tr>
<td>6 hrs</td>
<td>0</td>
<td>0.371</td>
</tr>
<tr>
<td>9 hrs</td>
<td>0</td>
<td>0.485</td>
</tr>
<tr>
<td>24 hrs</td>
<td>0</td>
<td>0.281</td>
</tr>
</tbody>
</table>

* Concentrations less than 0.25 ng/ml were undetectable by this method; these values were expressed as 0 for statistical analysis. Abbreviation: NA = not available.
Phylogenetic parameters were measured or assessed in triplicate for each stent placement, a measurement taken at each of three different sampling points along the stent’s length. These triplicate measurements were averaged for each stent. The mean group parameter values were then calculated for both the bare-metal and drug-eluting stent groups. These respective group means were statistically compared using the Student t-test for the analysis of unpaired data. In accordance with general practice in the literature, a similar statistical approach to that outlined earlier was taken in analyzing all parameters derived from the histological/morphological evaluation, whether the parameter represented a direct measurement, a calculated value derived from direct measurements, or an ordinal score. In all cases, two-tailed probability values were calculated and a probability value of less than 0.05 was considered statistically significant. All mean values are expressed as the mean ± the standard error of the mean, and all statistics were calculated using the Statview 5.01 statistical package for the Macintosh (SAS Institute, Inc., Cary, NC).

Results

Observations in Dogs

Stents were successfully implanted in the BAs of 16 dogs. At no time did any of the animals appear to have feeding or behavioral disorders. Formal neurological examinations were not conducted, but the animals exhibited unremarkable behavioral, gait, and feeding patterns throughout the study period.

Serum Sirolimus Concentration

The serum sirolimus concentration was assessed using blood samples obtained from a peripheral vein at the aforementioned time intervals. Sirolimus could not be detected in the peripheral blood later than 24 hours posttreatment in any of the animals. As shown in Table 1 and Fig. 2, in all but one animal sirolimus concentrations were undetectable after 9 hours (one dog had persistent levels at 24 hours).

Angiography Findings

Conventional angiography demonstrated patency of all parent vessels without evidence of binary restenosis (<50%, not including strut thickness). Decreased lumen diameters of the ostia of the perforating vessels were seen in three animals from the bare-metal stent group and one from the sirolimus-eluting stent group.

Histological and Computer-Assisted Morphometric Analysis

Sixteen stents were explanted (eight in each group). Sirolimus did not inhibit endothelialization of the treated stents (Fig. 3) compared with the bare-metal devices (p = 0.15). A trend toward lower inflammation scores was observed in the sirolimus group (Fig. 4) but did not reach statistical significance (p = 0.34). Compared with the bare-metal group (Fig. 5), significant SMC inhibition (p = 0.003) and increased intimal fibrin content (p < 0.0001) were seen in the sirolimus group. No stent-induced cell injury was demonstrated on histological analysis of specimens obtained in animals from either group, denoting both a lack of injury-induced vascular remodeling and an approximately 1:1 ratio between stent size and lumen diameter (that is, the stent was not oversized). The differences in the cerebrovascular response to sirolimus-coated compared with bare-metal stents are summarized and illustrated in Fig. 6, whereas the actual mean group parameter values are given in Table 2.

With the short duration of stent implantation and because no significant cell injury was induced by the implant itself, no statistically significant differences in restenosis parameters (neointimal area, lumen area, neointimal/media ratio, ne-...
intimal thickness, and percentage of occlusion) were observed between the two groups.

Examination of the brainstem sections obtained in both groups failed to demonstrate evidence of neurotoxicity such as infarction or gliosis (Fig. 7). Additionally, there was no histological evidence of vessel injury or pseudoaneurysm formation in either group.

Discussion

Recent advances in coronary stent technology have made it possible to deliver stents into the intracranial circulation, despite the significant tortuosities of these vessels. With the growing interest in stent-assisted angioplasty for intracranial atherosclerotic disease, clinicians are placing these devices in the intracranial circulation with increasing frequency but without an understanding of the effects of stents on side branches or parent vessels. In one recent prospective study, the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial, investigators have shown that stenosis of more than 50% occurred in 30% of intracranial arteries, with nearly 40% of the patients symptomatic, most likely as a result of recurrent stenosis. This rate of restenosis is not unexpected because intracranial vessels have a relatively high proportion (60–80%) of SMCs (the putative agent in stent-induced restenosis), with a paucity of adventitia. Clearly, these rates of symptomatic recurrent stenosis might preclude further use of intracranial stents for the management of intracranial atherosclerotic disease.

Because sirolimus inhibits cell cycle progression and the inflammatory cascade involved in cell recruitment, it is imperative to determine the effects of this drug on native intracranial vessels. Unlike the coronary vasculature, intracranial vessels have a paucity of adventitia and are bathed in CSF. Their fragility has raised some concerns regarding the safety of sirolimus in cerebral vessels. If vascular injury occurs as a result of the stent implantation, the potential exists for increased pseudoaneurysm formation or disruption of vessel integrity as a result of the impaired cell signaling (via cytokines). Additionally, if sirolimus leaches into the CSF through a transmural process, there are no data available regarding local drug effects on neural tissue. Although the potential for improved long-term vessel patency after stent placement exists, questions regarding neurotoxicity must be answered before implantation of these devices into human beings.

As we have demonstrated here, no obvious neurotoxicity was seen during the study period, regardless of which stent was implanted. Although no formal neurological examinations were performed, each animal was evaluated daily; no differences in feeding, gait, or behavior were apparent in either group of dogs. In addition to the clinical outcome of these animals, explanted brainstems failed to show evidence of tissue neurotoxicity such as gliosis or infarction.

**TABLE 2**

<table>
<thead>
<tr>
<th>Score</th>
<th>Bare-Metal</th>
<th>Sirolimus-Eluting</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of stents</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>histopathological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>endothelialization</td>
<td>3.000</td>
<td>2.709</td>
<td>0.154</td>
</tr>
<tr>
<td>inflammation</td>
<td>0.833</td>
<td>0.584</td>
<td>0.337</td>
</tr>
<tr>
<td>intimal fibrin</td>
<td>0.124</td>
<td>1.334</td>
<td>$&lt;0.0001^*$</td>
</tr>
<tr>
<td>intimal SMC</td>
<td>1.625</td>
<td>0.333</td>
<td>0.003*</td>
</tr>
<tr>
<td>morphometric findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>artery area (mm$^2$)</td>
<td>1.78</td>
<td>1.72</td>
<td>0.47</td>
</tr>
<tr>
<td>lumen area (mm$^2$)</td>
<td>1.03</td>
<td>0.97</td>
<td>0.52</td>
</tr>
<tr>
<td>neointima area (mm$^2$)</td>
<td>0.25</td>
<td>0.26</td>
<td>0.93</td>
</tr>
<tr>
<td>media area (mm$^2$)</td>
<td>0.26</td>
<td>0.23</td>
<td>0.41</td>
</tr>
<tr>
<td>neointima/media ratio</td>
<td>1.04</td>
<td>1.28</td>
<td>0.36</td>
</tr>
<tr>
<td>neointima thickness (mm)</td>
<td>0.07</td>
<td>0.07</td>
<td>0.78</td>
</tr>
<tr>
<td>occlusion (%)</td>
<td>19.58</td>
<td>21.19</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* Indicates statistical significance.
Sirolimus-eluting stents in the canine cerebral vasculature

Moreover, no evidence of neurotoxicity was identified on histological analysis of the explanted brainstems or vessels. No significant differences in vascular injury were seen in the explanted vessels obtained in either group. Although measurement of sirolimus concentration in CSF is important, obtaining samples would have placed the animals at significant risk because CSF would have been obtained from the cisterna magna while the animal was receiving an antithrombotic regimen consisting of heparin, clopidogrel, and aspirin. We therefore elected to determine CSF levels in future studies in which the measurements would not jeopardize the intent of the study, which in this case was to assess drug safety in the cerebral vasculature and neural tissue.

The time to endothelialization of implanted stents is an important factor when evaluating drug-eluting polymer coatings. Inhibition of endothelialization portends an increased embolic risk because the exposed stent is thrombogenic. Thus, thromboembolism may occur in patients receiving clopidogrel or another antiplatelet medication for a period of 1 month if incomplete endothelialization persists beyond 1 month. In this study, no significant differences were found in the mean endothelialization scores between the two groups (p = 0.15); endothelialization was not impaired.

The cascade of cell proliferation and cellular signaling begins immediately after endothelial injury resulting from stent-assisted angioplasty. This process enters into a chronic phase after approximately 4 weeks, which is the time when neointimal proliferation is demonstrated. Although levels of sirolimus in peripheral blood are not detectable beyond 24 hours, elution continues beyond 30 days, with approximately 80% elution by 30 days and 93% elution by 90 days in coronary models.13

In addition to the absence of inhibition of endothelialization, another benefit seen in the use of sirolimus was mitigation of SMC proliferation. Smooth-muscle cells have been reported to be responsible for in-stent stenosis. Although significant differences were found between groups (p = 0.003), neither one exhibited differences in neointimal area, the primary index of restenosis. This finding may be related to the lack of induced injury during implantation and the duration of stent implantation. Neointimal proliferation typically develops during the chronic remodeling phase, which begins 3 to 4 weeks after vessel wall injury. During this dynamic phase of remodeling, proteoglycan matrix deposition takes place until a steady state of resorption and deposition occurs, as well as proliferation and activation of SMCs. The benefit of sirolimus-coated stents is that the cell cycle is arrested, so proteoglycan and fibrin deposition takes place while SMC activation and proliferation are inhibited. This supposition was demonstrated in our study by the increased intimal fibrin deposition observed in dogs treated with coated stents compared with those treated with bare-metal devices (p < 0.0001).

In addition to symptomatic ischemia resulting from stent-induced stenosis, symptomatic brainstem ischemia may also result from perforating vessel stenosis in the BA (Fig. 8). Brainstem infarction can occur in a delayed fashion as a result of ischemia from compromised ostia of perforating vessels, which may result initially from “snowplowing” of plaque into these vessels, or from stent-induced ostial stenosis. According to the coronary literature, up to 19% of side branches become occluded following stent placement.5,10 This is caused by stent placement in parent vessels with preexisting ostial stenosis. A longer duration of implantation is necessary to understand the implications of these findings.

Conclusions

Sirolimus-coated stents have demonstrated the ability to inhibit in-stent stenosis in the coronary circulation. The mechanism of this macrolide antibiotic is well understood at the cellular level. It has been demonstrated that the net effect of sirolimus is to arrest cell cycle progression at the G1/S transition and to block SMC proliferation by binding to its intracellular FKBP12 receptor. The use of sirolimus-coated stents in the intracranial circulation may help reduce unacceptable rates of in-stent stenosis. Use of these coated stents has been precluded by fears of neurotoxicity to brain tissue and by the fragility of the intracranial vessels surrounded by CSF. Using an in vivo model to address the safety of sirolimus-coated stents in the intracranial circulation, we deter-

![Image](https://via.placeholder.com/150)

**Fig. 7.** Photomicrograph of a thin section of the brainstem showing normal tissue with no evidence of infarction or necrosis. Luxol fast blue stain, original magnification × 4.

**Fig. 8.** Photomicrograph showing reduction in the ostia of the perforating vessel due to an overlying strut and cellular neoproliferation between stent struts after treatment with a bare-metal stent. Metachromatic stain, original magnification × 8.9.
mired that these devices do not exhibit neurotoxic effects on the tissue or vessels during the 30-day period after implantation. Additionally, SMC proliferation is inhibited and endothelialization of the stent is not delayed. Our analysis of these findings indicates that sirolimus-coated stents may provide protection against symptomatic in-stent stenosis and are safe to use in the intracranial circulation. Future in vivo studies with a longer duration of implantation are needed to elucidate the effect of sirolimus-coated stents on restenosis of the cerebrovasculature.

Disclosure

The Department of Neurosurgery and Toshiba Stroke Research Center receive research support from Cordis Corp., and Dr. Hopkins is a consultant for Cordis Corp.

Acknowledgments

We thank Cordis Corp. for their support of our research, Paul H. Dressel for preparation of the illustrations, and the staff at Kaleida Gates Hospital Library for assistance with literature searches and obtaining reference articles.

References