Comparison of Primary Angioplasty With Stent Placement for Treating Symptomatic Intracranial Atherosclerotic Diseases

A Multicenter Study

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Background and Purpose—We sought to compare the clinical outcomes between primary angioplasty and stent placement for symptomatic intracranial atherosclerosis.

Methods—We retrospectively analyzed the clinical and angiographic data of 190 patients treated with 95 primary angioplasty procedures and 98 intracranial stent placements (total of 193 procedures) in 3 tertiary care centers. Stroke and combined stroke and/or death were identified as primary clinical end points during the periprocedural and follow-up period of 5 years. The rates of significant postoperative residual stenosis (≥50% of greater stenosis immediately after the procedure) and binary restenosis (≥50% stenosis at follow-up angiography within 3 years) were also compared. The comparative analysis was performed after adjusting for age, sex, and center.

Results—Fourteen procedures in the angioplasty-treated group (15%) and 4 in the stent-treated group (4.1%) had significant postoperative residual stenosis (relative risk [RR]=2.8, 95% CI, 0.85 to 9.5, P=0.09, for the adjusted model). There were 3 periprocedural deaths (1.5%), 1 in the angioplasty group (1.1%) and 2 in the stent-treated group (2.0%) and 14 periprocedural strokes (7.3%), 7 periprocedural strokes in each group (7.4% and 7.1%, respectively; hazard ratio=1.1; 95% CI, 0.57 to 1.9, P=0.85). Angiographic follow-up was available for 134 procedures (66 angioplasty-treated and 68 stent-treated cases). Forty-eight procedures (36.1%) had evidence of binary restenosis (25 of 66 angioplasties, 23 of 68 stents, P=0.85). Binary restenosis-free survival at 12 months was 68% for the angioplasty-treated group and 64% for the stent-treated group. There was no difference in follow-up survival (stroke, or stroke and/or death) between the angioplasty-treated and the stent-treated groups (hazard ratio=0.54; 95% CI, 0.11 to 2.5, P=0.44 and hazard ratio=0.50; 95%, CI 0.17 to 1.5, P=0.22, respectively, after adjusting for age, sex, and center). The stroke-and/or death-free survival at 2 years for the angioplasty-treated group and the stent-treated group was 92±4% and 89±5%, respectively.

Conclusions—Stent treatment for intracranial atherosclerosis may lower the rate of significant postoperative residual stenosis compared with primary angioplasty alone. No benefit of stent placement over primary angioplasty in reducing stroke or stroke and/or death could be identified in this study. (Stroke. 2008;39:2505-2510.)

Key Words: intracranial atherosclerosis ■ primary angioplasty ■ stroke ■ intracranial stenosis ■ restenosis ■ death ■ stent placement

Intracranial atherosclerosis accounts for 8% to 10% of ischemic strokes in large-population and hospital-based studies.1-3 The annual rate of recurrent stroke may be as high as 15% in these patients.1,4-8 Surgical treatment for prevention of stroke and death in patients with symptomatic intracranial stenosis has been largely abandoned since the failure of the External Carotid/Internal Carotid Artery Bypass Trial9 in 1985. The Warfarin versus Aspirin for Symptomatic Intracranial Disease Study did not show any benefit of anticoagulation over aspirin.10 Recurrent cerebral ischemic event rates in antithrombotic failure cases may reach as high as 56%.11 Percutaneous angioplasty for symptomatic intracranial stenosis, refractory to medical management, was initially reported in the 1980s.12,13 Since then and particularly during the past 2 decades, percutaneous angioplasty with or without
stent placement for symptomatic intracranial stenosis has been reported in a number of individual series and a few prospective multicenter trials.\textsuperscript{4,5,14–34} In the early 1990s, the development of newer-generation, more flexible, microballoon catheters intended for cerebrovascular use and smaller balloon-expandable stents, initially introduced for coronary applications, increased the technical success rates and increased the interest in these therapeutic options. Numerous recent reports have shown that both procedures (ie, angioplasty alone and stent placement) are technically feasible with success rates >90% and low periprocedural complications rates (range of 0% to 20%).\textsuperscript{5,14–24,35–37}

Some authors have proposed theoretical advantages of stent placement over primary angioplasty by preventing early elastic recoil and negative remodeling.\textsuperscript{38,39} A recent report of a comparison between angioplasty and stent placement in a small group of patients (N=24) suggested that stent placement may be better in terms of early and late lumen gain for intracranial stenosis.\textsuperscript{39} No other direct radiographic or clinical outcome comparisons are available in the literature to date. Here we have combined data from 3 major endovascular centers to compare the radiographic and clinical outcomes of both procedures.

Subjects and Methods

We conducted a retrospective analysis of clinical and radiographic characteristics of 190 patients and 193 procedures with intracranial stenosis at 3 endovascular surgical neuroradiology centers. All patients with intracranial stenosis treated by the endovascular approach at these centers were identified. Eighty-nine procedures were identified from the University of Iowa endovascular surgical neuro-radiology procedure database between 1999 and 2006. Forty-four patients were identified from the University of Medicine and Dentistry of New Jersey database between 2003 and 2006. Sixty patients were identified from Our Lady of Lourdes Regional Medical Center, Louisiana, between 1996 and 2004. The clinical and angiographic data of the New Jersey\textsuperscript{33} and Louisiana\textsuperscript{40} patients have been reported previously in separate publications.\textsuperscript{40}

Records were abstracted to obtain data on age, sex, stroke risk factors (hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, history of previous stroke/transient ischemic attack, and cigarette smoking), location of atherosclerotic lesion (anterior or posterior circulation), type of procedure performed (primary angioplasty or stent placement), preprocedural stenosis, postoperative residual stenosis immediately after the procedure, periprocedural complications, follow-up angiographic findings, and clinical outcomes at follow-up. Significant postoperative residual stenosis was defined as a stenosis $\geq50\%$ in the immediate postoperative angiographic images. Binary restenosis was defined as $\geq50\%$ stenosis at the time of angiographic follow-up after excluding postoperative residual stenosis. Significant postoperative residual stenosis and binary restenosis were identified as angiographic end points. Stroke and stroke and/or death were recorded as clinical end points. All major and minor strokes and death from all causes were included for this analysis. A large proportion of patients were scheduled for follow-up angiography between 6 and 18 months in the local endovascular neuroradiology center, after the initial procedure. The time interval for angiographic follow-up was recorded until either the angiographic end point was achieved or the last normal follow-up was performed, up to 36 months. All patients had clinical follow-up scheduled in the endovascular clinic at 3, 6, and 12 months. Asymptomatic patients had subsequent yearly follow-up visits. At the time of follow-up, patients were evaluated by a stroke neurologist and endovascular specialist. The time period for clinical follow-up was recorded until either the clinical end points were achieved or the last normal clinical follow-up was performed, up to 60 months, depending on the center. Short-term results included significant postoperative residual stenosis and periprocedural (30 day) stroke and death. Long-term results included binary restenosis and stroke and stroke and/or death rates at the time of angiographic and clinical follow-up.

All of the angioplasty procedures were included in “the angioplasty-treated group” and all stent placements were included in “the stent-treated group.” Patients in the angioplasty group who subsequently had a stent placed secondary to treatment failure (restenosis) were included in the angioplasty group for the clinical outcome analysis. For patients with binary restenosis who underwent repeat angioplasty, results of only the first procedure were included for angiographic outcomes.

Statistical Methods

We used the $\chi^2$ test to compare baseline demographic and clinical risk factors for categorical variables and rates of periprocedural stroke, death, and significant postoperative residual stenosis and the $t$ test for continuous risk factors between the angioplasty-treated and stent-treated groups. Association of periprocedural stroke, death, and residual stenosis were analyzed by a multivariate logistic regression to adjust for differences in age, sex, and center. The associations of binary restenosis, stroke, and stroke and/or death between the 2 groups were analyzed unadjusted and adjusted for age, sex, and center by Cox proportional-hazards analyses. We performed a Kaplan-Meier survival analysis of binary restenosis and stroke and/or death for both the angioplasty- and the stent-treated group. SAS version 9.13 (SAS Institute Inc, Cary, NC) was used for all statistical analyses, and R, version 2.6.0 (The R Foundation for Statistical Computing) was used to display graphics.

Results

A total of 193 intracranial atherosclerotic lesions were treated in 190 patients; 3 patients had procedures performed in 2 locations. A total of 95 angioplasty procedures and 98 stent placements were performed. The mean $\pm$SD age of the patients was 61.8 $\pm$12.7 years; 136 were men. The comparison of baseline characteristics between the 2 groups is provided in Table 1. Risk factors were reported for 2 centers. No significant differences were observed between the 2 groups, except that a higher proportion of patients at the University of Medicine and Dentistry of New Jersey underwent stent placement (60%) than primary angioplasty (32%).

Periprocedural Results

Angiographic Outcome

Fourteen procedures in the angioplasty-treated group (15%) and 4 in the stent-treated group (4.1%) had significant postoperative residual stenosis ($P=0.01$). The relative risk (RR) after adjustment for age, sex, and center was 2.8; 95% CI, 0.85 to 9.5; $P=0.09$.

Clinical Outcome

The rate of stroke and/or death during the periprocedural period (30 days) was 8.4% (8/95) in the angioplasty-treated group and 9.2% (9/98) in the stent-treated group (RR=0.81, 95% CI, 0.28 to 2.4, $P=0.70$) after adjusting for sex, age, and center. A total of 14 periprocedural strokes (7.3%) were recorded in 193 procedures. Seven strokes occurred in each of the 2 groups (7.3% and 7.1% in the primary angioplasty– and stent-treated patients, respectively). There were 3 periprocedural deaths (1.5%) in 193 procedures, 1 in the angioplasty-treated group (1.1%) and 2 in the stent-treated group (2.0%). Two deaths were due to vessel rupture resulting in subarachnoid hemorrhage, and 1 was caused by the initial stroke.
to 36 months) for the angioplasty-treated group and 8 months (range, 2 to 36 months) for the stent-treated group. A total of 47 (35.1%) procedures had evidence of binary restenosis at the time of follow-up. Twenty-five patients in the angioplasty-treated group (38.9%) had binary restenosis at the time of follow-up angiography compared with 23 patients in the stent-treated group (34%). After adjusting for age, sex, and center, there was no difference in the rate of binary restenosis between the angioplasty-treated and stent-treated groups (hazard ratio [HR] = 1.1; 95% CI, 0.6 to 1.9, P = 0.85; Table 2). Kaplan-Meier survival analysis revealed that binary restenosis-free survival for the angioplasty-treated group was 68 ± 6% at 12 months and for the stent-treated group was 64 ± 7% at 12 months (Figure 1).

**Clinical Outcome**

One hundred eighty-seven patients who survived the first month were followed up clinically. Median follow-up time for the angioplasty-treated patients was 16 months (range, 1 to 62 months) and for the stent-treated patients was 12 months (range, 1 to 52 months). There were a total of 7 strokes in both the angioplasty-treated and stent-treated patients, 3 (3%) in the angioplasty-treated and 4 (4%) in the stent-treated patients, and 7 deaths, 3 (3%) in angioplasty-treated and 4 (4%) in stent-treated patients, during the follow-up period, after excluding periprocedural stroke and death. Only 1 death was attributed to a neurologic cause. One patient died due to abdominal sepsis after surgery and 1 died due to primary lung cancer. Three deaths were attributed to acute coronary events. The cause of death was unknown in the remaining 2 patients. After adjusting for age, sex, and center, there was no difference in the rate of stroke (HR = 0.54; 95% CI, 0.11 to 2.5, P = 0.44) and stroke and/or death (HR = 0.50; 95% CI, 0.17 to 1.5, P = 0.22) between the angioplasty-treated and the stent-treated patients. The stroke- and/or death-free survival at 2 years was 92 ± 4% for the angioplasty-treated group and 89 ± 5% for the stent-treated group (Figure 2).

**Discussion**

The role of medical management for the treatment of symptomatic intracranial stenosis is not fully established. In the External

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**Table 1. Bivariate Comparison of Demographic, Clinical, and Angiographic Characteristics, and Peri-Procedural Events Between Primary Angioplasty–Treated and Stent-Treated Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Angioplasty-Treated (N=98)</th>
<th>Stent-Treated (N=95)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Iowa</td>
<td>30 (32%)</td>
<td>59 (60%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UMDNJ†</td>
<td>22 (23%)</td>
<td>22 (22%)</td>
<td></td>
</tr>
<tr>
<td>OLOL Louisiana‡</td>
<td>46 (45%)</td>
<td>14 (19%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>61.5 ± 13.0</td>
<td>62.3 ± 12.4</td>
<td>0.65</td>
</tr>
<tr>
<td>Women</td>
<td>62 (65%)</td>
<td>76 (78%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (40%)</td>
<td>54 (67%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>15 (29%)</td>
<td>26 (32%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>28 (54%)</td>
<td>34 (42%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (25%)</td>
<td>30 (37%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous stroke/transient</td>
<td>17 (33%)</td>
<td>30 (37%)</td>
<td>0.43</td>
</tr>
<tr>
<td>ischemic attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>17 (33%)</td>
<td>30 (37%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Anterior circulation (N=156)</td>
<td>42 (55%)</td>
<td>40 (50%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Pre-procedure stenosis (mean ± SD)</td>
<td>89.2 ± 11</td>
<td>90.1 ± 9</td>
<td>0.76</td>
</tr>
<tr>
<td>Residual stenosis (&gt;50%)</td>
<td>14 (15%)</td>
<td>4 (4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peri-procedural complications</td>
<td>8 (8%)</td>
<td>9 (9%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (7%)</td>
<td>7 (7%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Risk factors based on UMDNJ and University of Iowa, except for age and sex; †University of Medicine and Dentistry New Jersey; ‡Our Lady of Lourdes Regional Medical Center, Louisiana.

**Long-Term Results**

**Angiographic Outcome**

Angiographic follow-up was available for 134 procedures (66 in the angioplasty- and 68 in the stent-treated group). The median angiographic follow-up time was 12 months (range, 2

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**Table 2. The Association Between Treatment Modality (Primary Angioplasty or Stent Placement) With Clinical and Angiographic Outcomes**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Treatment Group</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Angioplasty</strong></td>
<td>Primary Angioplasty</td>
<td>1.0 (0.58–1.8) P = 0.93</td>
</tr>
<tr>
<td>Any stroke</td>
<td>Stent Placement</td>
<td>1.1 (0.57–1.9) P = 0.85</td>
</tr>
<tr>
<td>Median follow-up time in months</td>
<td>12 [2–36]</td>
<td>8 [1–36]</td>
</tr>
<tr>
<td><strong>Stroke and/or death</strong></td>
<td>Primary Angioplasty</td>
<td>0.49 (0.11–2.3) P = 0.36</td>
</tr>
<tr>
<td>Median follow-up time in months</td>
<td>16 [1–62]</td>
<td>12 [1–52]</td>
</tr>
</tbody>
</table>

*Adjusted by center, age and sex using Cox proportional hazard analyses.
Carotid/Internal Carotid Artery Bypass Trial, the medical group (treated with aggressive stroke risk factor management and 1300 mg of daily aspirin) had an annual mortality and stroke rate of 8% to 10%. The Warfarin versus Aspirin for Symptomatic Intracranial Disease Study Trial was prematurely halted because of the safety profile of the warfarin-treated group (greater incidence of hemorrhages) after randomizing 569 patients. The rates of ipsilateral ischemic stroke for the aspirin- and warfarin-treated groups were 12% and 11%, respectively, during a mean follow-up period of 1.8 years. Thijs and Albers reported that 52% of patients with intracranial atherosclerosis who had failed optimal antithrombotic therapy (antiplatelet agents, warfarin, or heparin) had recurrent ischemic events. Mazighi et al demonstrated a 2-year ischemic event recurrence rate in the stenotic vessel territory of 38.2% (13.7% strokes and 24.5% transient ischemic attacks), despite medical management. Other antiplatelet agents including clopidogrel, extended-release dipyridamole plus low-dose aspirin, and ticlopidine do not have sufficient data to support their use in primary or secondary stroke prevention for intracranial stenosis. Aggressive medical management of hypertension, diabetes mellitus, body mass index, hyperlipidemia, and cigarette smoking cessation has been suggested as an important part of optimal medical management, but these therapies lack sufficient data. The endovascular approach for treatment of intracranial disease may provide some potential benefit in selected patients who fail medical management.

We present the angiographic and clinical data of 190 patients with 193 symptomatic intracranial atherosclerotic lesions treated with either primary angioplasty or stent placement. Postoperative residual stenosis was seen more often in angioplasty-treated patients compared with stent-treated groups (12% and 11%, respectively, during a mean follow-up period of 1.8 years. Terada and colleagues demonstrated that 2 of 15 patients (13%) had significant postoperative residual stenosis with angioplasty treatment compared with none of 9 patients with stent treatment. Improved lumen gain was seen in the stent-treated patients compared to the angioplasty treated patients. We were unable to perform lumen gain analysis because of the unavailability of complete angiographic data for all patients. Similar observations of lumen gain have been made in the coronary literature. Stent placement, compared with angioplasty, conferred a larger postprocedural diameter in the
STRESS trial for coronary vessel atherosclerosis. Connors et al. reported a 16% incidence of significant postoperative residual stenosis after 50 angioplasty procedures. Marks et al. reported a much higher rate of significant postoperative residual stenosis in intracranial angioplasty series (18/36 cases, 50%). In contrast, Lylyk et al. found no significant postoperative residual stenosis in 104 intracranial stenting procedures.

Our data suggest that the rates of periprocedural stroke and death were similar in both groups. These may be comparable with periprocedural rates reported in the literature. Marks et al. demonstrated a periprocedural stroke and death rate of 8.3% (2 deaths, 1 stroke in 37 angioplasty procedures). Connors et al. reported a 6% (1 death, 2 strokes in 50 angioplasties) stroke and death rate during the “current period” of primary angioplasty procedures. Jiang et al. observed a periprocedural stroke rate of 6.6% (12/181 stent placements), including 2 asymptomatic intracranial hemorrhages. The periprocedural stroke rate in the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial was 6.6% (461 stent placements). There were no periprocedural deaths in the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial. A recently published single-arm multicenter study for symptomatic intracranial stenosis treated with the Wingspan stent system showed a periprocedural stroke and death rate of 4.5% (2/44). These authors also reported 10 asymptomatic diffusion-restricted lesions on magnetic resonance imaging scans obtained after the procedure. A US multicenter experience with the Wingspan system reported a periprocedural stroke and death rate of 6.1%. Those authors also noticed 10 asymptomatic cerebral lesions with restricted diffusion seen on follow-up magnetic resonance imaging scans.

We did not find any significant impact of primary angioplasty or stent placement on binary restenosis. Terada et al. was able to demonstrate that stent placement was associated with lower rates of binary restenosis compared with primary angioplasty in a small group of patients (4/15 in the angioplasty group and 0/9 in the stent-treated group). Long-term lumen gain was also improved in the stent-treated group. The difference in results between these studies could be explained by small sample size, sampling error, nonrandomization, and selection bias. Because both studies were retrospective, no clear differences can be discerned. Because it is technically difficult to navigate long stents through the tortuous intracranial circulation, optimal opposition of the stent to the underlying lesion may not always be possible. This discordance may set the stage for restenosis in long intracranial lesions.

We were unable to show a difference in clinical end points (stroke, stroke and/or death) between the angioplasty- and stent-treated groups. Only 1 death was attributed to neurologic causes. All other deaths were either unrelated or of unknown etiology. We also thought that the periprocedural complications might not truly represent the long-term effect of the 2 treatment modalities. For this reason, we excluded periprocedural complications while calculating the stroke- and death-free survival to better understand the long-term impact of the 2 treatment modalities. Two-year stroke- and/or death-free survival for the angioplasty group and the stent group was 92±4% and 89±5%, respectively, in our analysis. Marks and colleagues demonstrated a 5-year stroke-free survival of 83.1% in 120 patients undergoing intracranial angioplasty alone. Jiang et al. reported 3 strokes and 4 stroke and/or death events (6.5% and 8.8%, respectively) in a clinical follow-up of 46 patients treated with the intracranial Apollo stent system. Results of a Wingspan study showed that 2 of 43 patients (4.7%) had strokes at the 6-month follow-up, with no deaths.

We recognize a number of potential limitations in our study. This is a retrospective study involving a relatively small group of patients. The data were collected from 3 different centers, and differences in patient selection, interventional techniques, and periprocedural management might have led to intercenter variability. We attempted to adjust for this variability in the multivariate analyses. Because of the difference in follow-up times between the primary angioplasty and the stent-treated patients, we truncated our survival analysis to 2 years to ensure comparable follow-up. Because treatment allocation between angioplasty and stent placement was not randomized, it is conceivable that clinical and angiographic characteristics between the 2 treatment groups might be different. However, we were unable to demonstrate a difference in the frequency of cardiovascular risk factors in a subset analysis of available data from 2 centers (see Table 1). However, the treatment choice between primary angioplasty and stent placement might have been based on lesion location, tortuosity of the proximal vessels, and size of the vessel involved. These inherent differences might have affected the rates of clinical and angiographic end points independent of the treatment modality used. Because of the retrospective nature of the study, certain variables, such as time interval between symptom onset and treatment, the characteristics of target lesions, intraprocedural dissections, device failures, and presence of concomitant atherosclerotic lesions in other arteries, were not consistent or uniformly ascertained. This methodologic limitation may lead to under-estimation of asymptomatic events and other potential confounders in the comparison.

Our analyses suggest no difference in clinical outcomes between primary angioplasty and stent placement for symptomatic intracranial stenosis. However, a randomized, controlled trial may be required to compare the clinical efficacy of primary angioplasty with stent placement for symptomatic intracranial stenosis.

Disclosures

None.

References


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