Initial Experience of Platelet Glycoprotein IIb/IIIa Inhibition With Abciximab During Carotid Stenting
A Safe and Effective Adjunctive Therapy

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Background and Purpose—Abciximab has been shown to decrease periprocedural ischemic complications after coronary intervention. However, the adjunctive use of abciximab in carotid stenting has not been adequately studied. We sought to determine the efficacy and safety of abciximab in carotid stenting.

Methods—Carotid stenting was performed in 151 consecutive patients determined to be at high surgical risk by a vascular surgeon. Of these, 128 consecutive patients received adjuvant therapy with abciximab (0.25 mg/kg bolus before the lesion was crossed with guidewire and 0.125 μg · kg⁻¹ · min⁻¹ infusion for 12 hours.). A heparin bolus of 50 U/kg was given, and activated clotting time was maintained between 250 to 300 seconds. All patients received aspirin and thienopyridine. Procedural and 30-day outcomes were compared between the control (n=23) and abciximab (n=128) groups.

Results—The 2 groups had similar baseline characteristics. Procedural events were more frequent in the control group (8%; 1 major stroke and 1 neurological death) compared with the abciximab group (1.6%; 1 minor stroke and 1 retinal infarction; P=0.05). On 30-day follow-up, 1 patient presented with delayed intracranial hemorrhage in the abciximab group. There were no other major bleeding complications.

Conclusions—Adjunctive use of abciximab for carotid stenting is safe with no increase in the risk of intracranial hemorrhage. This adjunctive therapy with potent glycoprotein IIb/IIIa inhibition may help to reduce periprocedural adverse events in patients undergoing carotid stenting. (Stroke. 2001;32:2328-2332.)

Key Words: carotid arteries ▪ platelets ▪ stents

Percutaneous endovascular intervention, especially with stenting, leads to significant platelet activation at the site of intervention.¹⁻³ The activated platelets contribute to the risk of thromboembolism at the time of procedure and increase the risk of acute or subacute thrombosis after stenting.⁴ Furthermore, procedural microembolization may lead to platelet activation in the distal microvasculature, which in turn may lead to ischemic complications. Activated platelets also initiate the cascade of events that may contribute to the risk of restenosis.⁵

Multicenter randomized trials have conclusively demonstrated the efficacy of platelet inhibition with glycoprotein (GP) IIb/IIIa receptor antagonists in reducing irreversible ischemic complications at the time of coronary intervention.⁶⁻⁷ Moreover, the bleeding risk with the use of these agents in percutaneous coronary revascularization procedures has been acceptable even when used in conjunction with weight-adjusted heparin, aspirin, and ADP receptor antagonists.⁶⁻⁷

Percutaneous stenting of the carotid arteries has emerged as a potential treatment alternative for symptomatic and asymptomatic carotid stenosis. The major concern regarding this form of therapy has been the risk of thromboembolism. To minimize the risk of stroke, pharmacological and mechanical approaches are currently being investigated. Considering the success of GP IIb/IIIa inhibitors in reducing ischemic complications during coronary interventions, it is logical to postulate potential benefit of such therapy in carotid stenting. However, there is substantial concern that risk of intracranial hemorrhage may be increased with GP IIb/IIIa inhibition. Currently, reliable safety and efficacy data for the use of GP IIb/IIIa in carotid stenting are lacking.

Accordingly, we sought to determine the safety and efficacy of platelet GP IIb/IIIa receptor inhibition with abciximab at the time of carotid stenting. In this series, we report the initial experience with abciximab in patients at high surgical risk undergoing carotid stenting.
Subjects and Methods

Study Population
We studied 151 consecutive patients between February 1998 and December 1999 undergoing carotid stenting of 159 arteries. Between February 1998 and July 1998, 23 consecutive patients (25 arteries) underwent carotid stenting without the adjunctive use of abciximab. This group was defined as the control group for our study analysis. In July 1998, adjunctive therapy with abciximab was initiated in all patients undergoing carotid stenting. The active treatment group included 128 consecutive patients (134 arteries) who were stented with adjuvant therapy with abciximab. All patients were treated with a similar procedural technique by a single experienced operator.

Patients were enrolled in the study according to a study protocol approved by the Institutional Review Board. A vascular surgeon screened all patients, and only patients deemed to be at high risk for carotid endarterectomy were considered for carotid stenting. All asymptomatic patients had stenosis $\geq 80\%$, and all symptomatic patients had stenosis $\geq 70\%$ as determined by the North American Symptomatic Endarterectomy Trial criteria. 9

Study Protocol
All patients received a heparin (50 U/kg) bolus followed by abciximab (0.25 mg/kg bolus, followed by 0.125 $\mu$g · kg$^{-1}$ · min$^{-1}$ infusion for 12 hours) before the lesion was crossed. Activated clotting time was checked after abciximab bolus and further heparin bolus was given if the activated clotting time was $<250$ seconds. All patients received aspirin 325 mg/d. Patients were treated with either ticlopidine (250 mg BID) or clopidogrel (75 mg/d) after the stenting procedure. Details of the carotid artery stenting procedure have been previously given. 9

Study End Points
Study end points included any stroke (major or minor), intracranial hemorrhage, and neurological death within 30 days. Minor stroke was defined as a new neurological deficit that resolved completely within 7 days or increased the National Institute of Stroke Scale (NIHSS) score by $\geq 4$. Major stroke was defined as a new neurological deficit that persisted after 7 days or increased the NIHSS score by $\geq 4$. Neurological death was defined as a death for which the proximate cause of death was related to stroke or intracranial hemorrhage. Bleeding complications were also determined to assess the safety of potent platelet GP IIb/IIIa receptor inhibition during carotid stenting.

Statistical Analysis
Categorical variables are expressed as frequencies and percentages, whereas continuous variables are presented as mean±SD. Fisher’s exact and $\chi^2$ tests were used to analyze nominal data. To compare continuous data, a $t$ test or Wilcoxon’s test was used, depending on the distribution of the data.

Results

Patient Population
The clinical characteristics of patients undergoing carotid stenting with and without abciximab were comparable (Table 1). Age and sex distributions were similar in both groups. More than half of the patients were symptomatic, with a higher proportion of patients with transient ischemic attack in the control group. Diabetes mellitus was present in one third of the patients. Most patients had coexisting coronary artery disease.

The comorbidities of the patients are listed in Table 2 and were similar in the 2 study groups. Coexistent severe cardiac disease was the most frequent comorbidity responsible for the high risk for carotid endarterectomy. Severe aortic stenosis (aortic valve area $<1.0$ cm$^2$), severe left ventricular systolic dysfunction, and severe coronary artery disease were the most frequent cardiac lesions. Patients were also referred for a percutaneous procedure as a result of previous neck surgeries, including radical neck dissection, neck irradiation, or prior carotid endarterectomy.

Procedural Outcome
Procedural complications were defined as all events occurring from the start of the intervention through hospital discharge. One patient had only angioplasty because stent deployment was not possible. Wallstent (Boston Scientific) and SMART (Cordis) stents were most frequently used. All patients had a technically successful procedure with $<20\%$ residual stenosis. Wallstents were more frequently used in the control group, whereas SMART stents were most frequently used in the abciximab-treated group (Table 3).

In the control group, 2 patients (8\%) had strokes during the procedure. Both these patients received selective infusion of abciximab and underwent carotid stenting with and without abciximab were comparable (Table 1).
**TABLE 3. Lesion Characteristics and Procedural Details**

<table>
<thead>
<tr>
<th>Lesion Characteristic</th>
<th>Control n (%)</th>
<th>Abciximab n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lesion location, n (%)</td>
<td>25</td>
<td>134</td>
<td>0.25</td>
</tr>
<tr>
<td>ICA</td>
<td>20 (80)</td>
<td>135 (86)</td>
<td>0.25</td>
</tr>
<tr>
<td>CCA</td>
<td>5 (20)</td>
<td>18 (14)</td>
<td>0.11</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>5.7±0.6</td>
<td>5.6±0.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Prestenosis</td>
<td>87±9</td>
<td>83±9</td>
<td>0.11</td>
</tr>
<tr>
<td>Poststenosis</td>
<td>3±5</td>
<td>3±7</td>
<td>0.71</td>
</tr>
<tr>
<td>Ulcer, n (%)</td>
<td>9 (36)</td>
<td>40 (30)</td>
<td>0.66</td>
</tr>
<tr>
<td>Stent, n (%)</td>
<td>Wall</td>
<td>19 (76)</td>
<td>55 (41)</td>
</tr>
<tr>
<td></td>
<td>SMART</td>
<td>1 (4)</td>
<td>58 (46)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5 (20)</td>
<td>20 (13)</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time.

urokinase into the middle cerebral artery with a microcatheter. One patient partially recovered, and the other patient died of intracranial hemorrhage. In the abciximab treatment group, 1 patient had stroke with sensory loss in contralateral upper extremity. One patient had permanent quadrantanopsia from retinal infarction. The procedural event rate in the abciximab-treated group was significantly lower compared with that of the control group (8% versus 1.6%, P=0.05; Table 4).

**Thirty-Day Outcome**

All events occurring from hospital discharge to 30 days from the intervention were included in the 30-day follow-up. One patient who had been treated with abciximab presented with a severe headache 4 days after the procedure. She was found to have a small intracranial hemorrhage at the site of a previous stroke. This patient recovered with conservative management. There were no further neurological events in the control group. On long-term follow-up, 2 patients in the control arm and 5 patients in the abciximab treatment arm died as a result of nonneurological causes (Table 4).

**Discussion**

No major bleeding complications were encountered in this study. Two patients in the abciximab and 1 patient in the control group developed a femoral artery pseudoaneurysm at the puncture site, requiring thrombin injection. Three patients in the abciximab group dropped their platelet count to <100 000 on the next day, but none had any bleeding complications. One of these patients developed a platelet count <50 000 and required platelet transfusion. There were no patients with thrombocytopenia in the control group.

**TABLE 4. All Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Control (n=23)</th>
<th>Abciximab (n=128)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural, n (%)</td>
<td>Major stroke</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Minor strokes</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Retinal infarct</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>ICH</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Death (neurological)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Total events</td>
<td>2 (8)</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>New events at 30 d, n (%)</td>
<td>Minor stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Major strokes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ICH</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stent thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Death (neurological)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Death (nonneurological)</td>
<td>2 (8)</td>
<td>5 (3.7)</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage; MI, myocardial infarction; AS, aortic stenosis; CAD, coronary artery disease; CLL, chronic lymphocytic leukemia; PE, pulmonary embolism; CHF, congestive heart failure; and OHT, orthotopic heart transplant.

The increased signals are noticed with each maneuver; however, stent deployment and high-pressure inflation to

abciximab. The study demonstrates that the use of abciximab is safe and is not associated with an excess risk of intracranial bleeding. Furthermore, the use of a platelet GP IIb/IIIa inhibitor along with aspirin and a thienopyridine is associated with a very low risk of ischemic complications during the intervention and a negligible risk of stent thrombosis during follow-up.

Inhibition of platelet aggregation by blockade of the platelet surface GP IIb/IIIa receptor with abciximab, a monoclonal-antibody Fab fragment, has been demonstrated to reduce the incidence of periprocedural ischemic complications among patients undergoing coronary interventions. The major action is postulated to occur in the distal microvasculature, where the activated platelets initiate the cascade of events leading to tissue hypoperfusion. The benefit derived from the prevention of procedural thromboembolism and resultant myonecrosis is persistent on long-term follow-up. This has led to widespread use of this therapy during coronary interventions. Compared with coronary intervention, embolization and platelet activation from carotid stenting can have an even more devastating impact on the functional status of the end organ.

Multiple studies using transcranial Doppler have demonstrated a significant incidence of microembolization during carotid endarterectomy. Studies using transcranial Doppler have also demonstrated high-intensity transients presumed to be echogenic particles during various steps of carotid stenting. The increased signals are noticed with each maneuver; however, stent deployment and high-pressure inflation to
postdilig the stents are associated with the most significant embolization. Recent evidence from the use of emboli protection devices proves that significant plaque material is dislodged during angioplasty and stenting of coronary and carotid arteries and saphenous vein grafts. Embolization of this material may lead to activation of platelets in the microcirculation, leading to more extensive organ damage.

This study demonstrates that adjuvant treatment with abciximab does not lead to a greater risk of intracranial bleeding. The efficacy of such treatment was compared with a control group. The use of historical control subjects is valid for the following reasons: (1) The patients in the control group had clinical characteristics similar to those of the patients treated with abciximab; (2) because abciximab was used in each consecutive patient, selection bias was not present; (3) the technique of carotid stenting was the same in both groups of patients, and an interventionist experienced in carotid intervention performed all procedures; and (4) other series reporting ≥50 patients undergoing carotid stenting have had an event rate similar to that of our control group (Table 5).

The periprocedural ischemic complication rate has been reported to be between 1.8% and 4.8% and between 0% and 4.3% on 7- to 30-day follow-up. In our series, abciximab lowered the periprocedural stroke rate to <2% without increasing the risk of intracranial hemorrhage. This extremely low rate of ischemic complications is likely due to decreased activation of platelets in the microvasculature after embolization of atheromatous debris.

Study Limitations
This is a single-center experience of consecutive patients undergoing carotid stenting with abciximab pretreatment. It describes the safety of abciximab, but the efficacy of such treatment has been inferred from a small control group in which abciximab pretreatment was not used. The overall event rate is low, precluding a multivariate analysis.

The study population is a unique, high-risk patient cohort. From this report, the risk-to-benefit ratio of abciximab in lower-risk patients cannot be generalized. Furthermore, the impact of such therapy on the cost of carotid stenting remains unknown. It is important to study the relative benefit and interaction of emboli protection devices with GP IIb/IIIa inhibition.

In conclusion, this is the first large series to study the safety of abciximab in carotid interventions. Use of abciximab appears safe and efficacious during carotid stenting. Prospective, randomized trials are needed, however, to prove the efficacy of this adjuvant therapy and to determine the relative risk reduction conferred by abciximab.

Acknowledgment
We would like to thank Kathy Hughes and Jake Schneider for their indefatigable help in maintaining the carotid stenting database.

<table>
<thead>
<tr>
<th>Study</th>
<th>Lesions, n</th>
<th>Technical Success, n (%)</th>
<th>30-d Outcome, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietrich et al17</td>
<td>117</td>
<td>116 (99.1)</td>
<td>Stroke: 10 (8.3)</td>
</tr>
<tr>
<td>Henry et al18</td>
<td>174</td>
<td>173 (99.4)</td>
<td>MI: 0 (0.0)</td>
</tr>
<tr>
<td>Laborde et al19</td>
<td>87</td>
<td>87 (100)</td>
<td>Death: 1 (0.9)</td>
</tr>
<tr>
<td>Wholey et al20</td>
<td>114</td>
<td>108 (95)</td>
<td>Stroke: 4 (3.5)</td>
</tr>
<tr>
<td>Shawl et al21</td>
<td>96</td>
<td>96 (100)</td>
<td>MI: 3 (3.1)</td>
</tr>
<tr>
<td>Yadav et al22</td>
<td>126</td>
<td>126 (100)</td>
<td>Death: 8 (6.3)</td>
</tr>
<tr>
<td>Global experience23</td>
<td>3129</td>
<td>3091 (98.8)</td>
<td>Stroke: 121 (3.9)</td>
</tr>
</tbody>
</table>

In Table 5, the periprocedural ischemic complication rate has been reported to be between 1.8% and 4.8% and between 0% and 4.3% on 7- to 30-day follow-up. In our series, abciximab lowered the periprocedural stroke rate to <2% without increasing the risk of intracranial hemorrhage. This extremely low rate of ischemic complications is likely due to decreased activation of platelets in the microvasculature after embolization of atheromatous debris.

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