Intracerebral Hemorrhages Associated With Neurointerventional Procedures Using a Combination of Antithrombotic Agents Including Abciximab

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Background—We report the occurrence of fatal intracerebral hemorrhage associated with using a combination of antithrombotic agents, including abciximab, in patients undergoing neurointerventional procedures.

Summary of Report—Seven patients (average age 60, range 46 to 73 years) developed fatal intracerebral hemorrhages associated with neurointerventional procedures and the use of intravenous abciximab. The procedures included angioplasty and stent placement in the cervical internal carotid artery (n = 4), angioplasty of the intracranial internal carotid artery (n = 1), and angioplasty of the middle cerebral artery (n = 2). Clinical deterioration was observed within 1 hour of the procedure in 5 patients and 7 and 8 hours after the procedure, respectively, in the remaining 2 patients. All patients had received heparin and clopidogrel; 6 had also received aspirin.

Conclusions—Intracerebral hemorrhages can occur after neurointerventional procedures in patients with recent cerebral ischemic events, particularly when aggressive antithrombotic treatment is used. (Stroke. 2002;33:1916-1919.)

Key Words: abciximab • angioplasty • carotid stenosis • intracerebral hemorrhage • stents

Agressive antithrombotic treatment is used as adjuvant to angioplasty and/or stent placement to reduce the rate of ischemic and thrombotic complications associated with these procedures. Intravenous abciximab, an antibody Fab fragment (c7E3 Fab) directed against platelet IIb/IIIa receptors that inhibit platelet aggregation, has been recently introduced to reduce the rate of ischemic complications associated with angioplasty and atherectomy for atherosclerotic lesions. Intravenously administered abciximab has a short half-life of 10 minutes, but its inhibitory effect on platelets lasts for 48 hours. The use of abciximab was first evaluated in a prospective, randomized, double-blind trial consisting of 2099 patients undergoing high-risk coronary intervention. Study patients received either a bolus and an infusion of abciximab. In the group given abciximab alone, ischemic complications of coronary angioplasty and atherectomy were significantly reduced. However, bleeding episodes and transfusions were more frequent in this group. Among all study patients, 6 patients had intracranial hemorrhages. Of these, 2 patients received placebo alone, 1 patient received an abciximab bolus, and 3 patients were assigned to receive the abciximab bolus and infusion (1 of these 3 did not receive the drug because the hemorrhage occurred after randomization but before angioplasty). The beneficial reduction in ischemic complications demonstrated in coronary interventions has led to frequent use of intravenous abciximab as an adjunct to neurointerventional procedures. Recent unpublished accounts of intracerebral hemorrhages associated with the use of antithrombotic medications during neurointerventional procedures have prompted us to report our pertinent experience.

Subjects and Methods

A report was compiled based on the clinical experience of neurointerventionists at 3 academic medical centers between 1999 and 2000. At each center, patients received intravenous abciximab in a single 0.25 mg/kg bolus followed by a 10-μg/minute infusion for a period of up to 8 hours. In 1 patient (patient 7), only the abciximab bolus was administered. The criteria used for administration of intravenous abciximab varied between treating physicians. In general, the patients undergoing the procedure were considered at high risk for peri procedure ischemic complications based on recent ischemic symptoms and/or morphological characteristics of the lesion. The following information was recorded for each patient: age; gender; preexisting risk factors including hypertension, hyperlipidemia, smoking, coronary artery disease, and peripheral vascular disease; presenting symptoms, interval between last ischemic symptom and procedure, findings on CT or MRI, if performed before procedure; severity and characteristics of lesion on angiography; dose of heparin and maximum activated coagulation time during the procedure; use of other thrombolytic agents or antiplatelet drugs; timing of onset and location of any intracerebral hemorrhage; and associated management, including repeat CT imaging, if any; and outcome.
Results
Seven patients (average age, 60; range, 46 to 73 years) developed fatal intracerebral hemorrhages associated with using a combination of antithrombotic agents, including abciximab, as an adjunct to neurointerventional procedures (Table). All patients had experienced recent ischemic symptoms ranging from 1 day to 2 weeks before the procedure. The procedures included angioplasty and stent placement in the cervical internal carotid artery (n = 4), angioplasty of the intracranial internal carotid artery (n = 1), and angioplasty of the middle cerebral artery (n = 2). Intravenous heparin boluses (15 to 67 U/kg) were used in 6 patients, and 1 patient had been placed on a heparin drip of 800 U/h 1 day before the procedure. Each patient had received clopidogrel either in combination with aspirin (n = 6) or alone (n = 1) before the procedure. Two patients (patients 2 and 7) were given an oral bolus dose of clopidogrel (300 mg) within the 24-hour period before the procedure. Clinical deterioration was observed within 1 hour of the procedure in 5 patients and 7 and 8 hours after the procedure, respectively, in 2 patients. CT imaging revealed 4 lobar hemorrhages, 2 basal ganglionic hemorrhages, and 1 hemorrhage that involved both regions. Representative images are shown in Figure 1. Rapid clinical deterioration was observed in all patients, despite platelet transfusions and methylprednisolone and/or protamine administration (Table). A repeat CT scan in each of 4 patients (patients 1 to 4) demonstrated expansion of the intracerebral hematoma. Representative images are shown in Figure 2. Three patients died within 24 hours, and another 3 died between 24 and 48 hours after the procedure; 1 patient died on the third day after the procedure.

Discussion
Our experience suggests that the use of intravenous abciximab in conjunction with aspirin, a thienopyridine derivative (clopidogrel), and heparin as an adjunct to neurointerventional procedures can result in rapidly progressive intracerebral hemorrhages. The exact proportion of intracerebral hemorrhages associated with intravenous abciximab is not documented in the literature. In a previous report of 37 patients who received intravenous abciximab during high-risk carotid angioplasty and stent placement, 2 patients developed hemorrhagic stroke. One patient developed an intraparenchymal hemmorhage (2.7%), and another developed a hemorrhagic infarct (2.7%). (The patient with the intraparenchymal hemorrhage is included in the present series [patient 3 in Table].) In the same study, 33 patients undergoing low-risk carotid angioplasty and stent placement received standard heparin therapy. No intracerebral hemorrhages were observed among the lower risk group; however, the groups were not comparable. Intracerebral hemorrhage has been reported in neurointerventional procedures that did not involve the use of abciximab. Morrish et al reported 4 intracranial hemorrhages (4.4%) in 90 patients who underwent angioplasty and stent placement for extracranial carotid stenosis. None of the patients had received abciximab, but all had received aspirin, a thienopyridine derivative (ticlopidine or clopidogrel), and heparin. It should be recognized that the present report is an observation consisting of a number of uncontrolled variables.

Therefore, the exact cause-effect role of abciximab in intracerebral hemorrhage during neurointerventional procedures is not clear.

Akkerhuis et al evaluated the risk of hemorrhagic stroke associated with intravenous abciximab use among patients undergoing percutaneous coronary intervention. A combined analysis of 4 double-blind, placebo-controlled, randomized trials was performed. A total of 8555 patients undergoing percutaneous coronary intervention were randomized to receive either a bolus and an infusion of abciximab (n = 5476) or a placebo (n = 3079). The risk of hemorrhagic stroke was 0.15% in patients treated with abciximab versus 0.10% in those treated with placebo. Among patients treated with abciximab, the rate of hemorrhagic stroke was higher in patients receiving standard-dose heparin than in those receiving low-dose heparin (0.27% versus 0.04%).

A higher rate of intracerebral hemorrhage seems to be associated with neurointerventional procedures than with coronary interventional procedures. One possible explanation is that patients undergoing neurointerventional procedures have usually experienced recent ischemic events. Ischemia that has effected the integrity of the blood-brain barrier could potentially lead to an increased likelihood of intracerebral hemorrhage. However, an increased risk of intracerebral hemorrhage was not observed in a randomized trial evaluating the efficacy of intravenous abciximab in ischemic stroke. In this trial, 74 patients with ischemic stroke presenting within 24 hours of symptom onset were treated with escalating doses of abciximab (n = 54) or placebo (n = 20). Asymptomatic intraparenchymal hemorrhages were detected by means of postprocedural CT imaging in 4 (7%) of 54 abciximab-treated patients and 1 (5%) of 20 placebo-treated patients. Another factor that may contribute to intracerebral bleeding is reperfusion injury. All patients included in our series had high-grade extracranial or intracranial occlusive vascular disease. The presence of flow-limiting lesions can lead to vasodilation and impaired autoregulation within the intracranial vascular bed. Reperfusion intraparenchymal hemorrhages have been described after carotid endarterectomy as a result of increased regional cerebral blood flow through vascular beds in conjunction with altered autoregulation. Meyers et al reported 7 (5%) of 140 patients who developed clinical and/or radiological manifestation of cerebral hyperperfusion syndrome after percutaneous angioplasty and stenting of craniovascular arteries. Intraparenchymal hemorrhages were observed in 2 of these 7 patients. One additional factor that may contribute to reperfusion injury is the release of microemboli from the site of carotid angioplasty and stent placement. The exact effect of microemboli on the distal cerebral microcirculation is unknown but might add to ischemic and/or hemorrhagic injury within cerebral tissue. Elevated systemic blood pressure has been reported to predispose to reperfusion injury. Although elevated blood pressure was frequently documented before the intracerebral hemorrhage in the present series, usually at the time of deterioration, the exact cause-effect relationship was not clear. The elevated blood pressure could have predisposed to the intracerebral hemorrhage; however, the elevated blood pressure may be a systemic response to intracerebral hemor-
rhage. Standard doses of aspirin, clopidogrel, and abciximab were used in the present series.\textsuperscript{4,12} Detailed measures of coagulation and platelet aggregation were not obtained at the time of intracerebral hemorrhage. Therefore, we cannot comment on the role of individual variations in response to antithrombotic medications as a predisposing factor for intracerebral hemorrhage.

A risk of intracerebral hemorrhage exists among the patients with recent cerebral ischemic events undergoing neurointerventional procedures, particularly when aggressive antithrombotic treatment is used.

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<tr>
<th>Pt</th>
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<th>Procedure Performed and Interval from Last Ischemic Symptom</th>
<th>Lesion Characteristics*</th>
<th>Other Antiplatelet Agents with Dose Used</th>
<th>Heparin Dose (U/kg) and ACT (s)</th>
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<tr>
<td>1</td>
<td>73/M</td>
<td>Hypertension hyperlipidemia</td>
<td>Transient ischemic attack</td>
<td>Angioplasty, MCA 4 days after transient ischemic attack</td>
<td>67% smooth calcified</td>
<td>Clopidogrel (75 mg/d), aspirin (325 mg/d)</td>
<td>53 (411s)</td>
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<tr>
<td>2</td>
<td>54/F</td>
<td>Previous smoking</td>
<td>Transient ischemic attack, SPECT showed decreased perfusion in ipsilateral hemisphere</td>
<td>Angioplasty, MCA 1 day after transient ischemic attack</td>
<td>70% irregular lesion</td>
<td>Clopidogrel (300 mg bolus), aspirin (325 mg/d)</td>
<td>33 (328s)</td>
</tr>
<tr>
<td>3</td>
<td>66/F</td>
<td>Hypertension, previous smoking, hyperlipidemia</td>
<td>Minor ischemic stroke, hypodensity in ipsilateral lenticular nucleus (5 mm) on CT</td>
<td>Angioplasty and stenting, cervical ICA 2 days after ischemic stroke</td>
<td>Pseudo-occlusion irregular, ulcerated, calcified lesion</td>
<td>Clopidogrel (75 mg/d), aspirin (325 mg/d)</td>
<td>67 (356s)</td>
</tr>
<tr>
<td>4</td>
<td>56/M</td>
<td>Hypertension, coronary artery disease, peripheral vascular disease</td>
<td>Transient ischemic attack</td>
<td>Angioplasty and stenting, cervical ICA 4 days after transient ischemic attack</td>
<td>90% irregular, ulcerated, calcified lesion</td>
<td>Clopidogrel (75 mg/d), aspirin (325 mg/d)</td>
<td>67 (180s)</td>
</tr>
<tr>
<td>5</td>
<td>61/M</td>
<td>Coronary artery disease, peripheral vascular disease, previous stroke</td>
<td>Minor ischemic stroke, multiple small old infarcts in ipsilateral hemisphere on CT</td>
<td>Angioplasty and stenting, cervical ICA 2 weeks after ischemic stroke</td>
<td>90% irregular, ulcerated, calcified lesion</td>
<td>Clopidogrel (75 mg/d), aspirin (325 mg/d)</td>
<td>58 (320s)</td>
</tr>
<tr>
<td>6</td>
<td>63/F</td>
<td>Hypertension</td>
<td>Minor ischemic stroke Infarction (watershed distribution) in ipsilateral frontal lobe on MRI</td>
<td>Angioplasty, intracranial ICA 2 days after ischemic stroke</td>
<td>75% irregular, long lesion</td>
<td>Clopidogrel (75 mg/d)</td>
<td>15 (not available)</td>
</tr>
<tr>
<td>7</td>
<td>46/F</td>
<td>Hypertension, smoking</td>
<td>Transient ischemic attack</td>
<td>Angioplasty and stenting, cervical ICA 1 day after transient ischemic attack</td>
<td>80% lesion</td>
<td>Clopidogrel (300 mg bolus), aspirin (325 mg/d)</td>
<td>800 U/hr (273s)</td>
</tr>
</tbody>
</table>

*% stenosis expressed as a ratio of diameters of stenotic segment and distal intact segment.

ACT indicates activated coagulation time; MCA, middle cerebral artery; N/A, not available; ICA, internal carotid artery; Pt, patient; MRI, magnetic resonance imaging; CT, computed tomography; SPECT, single photon emission computed tomography; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; M, male; F, female.

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**Figure 1.** A and B, Representative images of CT scanning performed 15 minutes after completion of the procedure in a 66-year-old woman who underwent cervical internal carotid artery angioplasty and stent placement (patient 3) and later demonstrated new focal deficits.

**Figure 2.** A and B, Comparable images after the scan was repeated (1 hour later), following clinical deterioration (patient 3). The images demonstrate the rapid expansion of a basal ganglionic hematoma.
Continued

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<th>Time to Hemorrhage and Interim Maximum Blood Pressure Recorded</th>
<th>Location of ICH</th>
<th>Treatment Given</th>
<th>Time to Death</th>
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<tr>
<td>15 min (systolic 200 mm Hg) Basal ganglia</td>
<td>Protamine, platelet transfusion</td>
<td>24–48 h</td>
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<td>30 min (systolic 185 mm Hg) Lobar</td>
<td>Protamine, platelet transfusion, methylprednisone</td>
<td>&lt;24 h</td>
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<tr>
<td>1 h (systolic 165 mm Hg) Lobar and basal ganglia</td>
<td>Protamine, platelet transfusion</td>
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<tr>
<td>8 h (systolic 199 mm Hg) Basal ganglia and IVH</td>
<td>Protamine, platelet transfusion</td>
<td>24–48 h</td>
<td></td>
</tr>
<tr>
<td>10 min (systolic 187 mm Hg) Lobar and IVH</td>
<td>Protamine, methyl prednisone</td>
<td>49–72 h</td>
<td></td>
</tr>
<tr>
<td>7 h (mean arterial pressure 143 mm Hg) Lobar</td>
<td>Protamine, platelet transfusion, methylprednisone</td>
<td>24–48 h</td>
<td></td>
</tr>
<tr>
<td>1 h (systolic 260 mm Hg) Lobar</td>
<td>Protamine, platelet transfusion</td>
<td>&lt;24 h</td>
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</table>

References
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