Multimodal Therapy for the Treatment of Severe Ischemic Stroke Combining GPIIb/IIIa Antagonists and Angioplasty After Failure of Thrombolysis

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Background and Purpose—Intraarterial and intravenous thrombolysis are often ineffective for the treatment of acute ischemic stroke and are associated with a significant risk of intracranial hemorrhage (ICH). Multimodal rescue therapy combining mechanical disruption and platelet GPIIb/IIIa receptor antagonists may improve recanalization.

Methods—Patients who did not recanalize with thrombolysis were treated with GPIIb/IIIa antagonists, angioplasty, or an embolectomy device. Treatment was individualized based on vascular anatomy, stroke mechanism, patient status, and symptom duration.

Results—Twelve patients were treated within 3.8 ± 2.2 hours. The mean National Institutes of Health Stroke Scale (NIHSS) score was 19.4 ± 4.1. Six patients had carotid terminus occlusion, whereas 5 had middle cerebral artery and 1 had basilar artery occlusion. The average doses of intraarterial tPA and reteplase were 17.1 ± 8.6 mg and 2 ± 0.6 units, respectively. All patients received either an intravenous or intraarterial abciximab bolus (mean 11.8 ± 5.8 mg) and heparin (mean 3278 ± 1716 U). Eleven were treated with angioplasty and 4 had mechanical embolectomy or stenting. Complete (8) or partial (3) recanalization was achieved in 11 cases. There was only one (8.3%) symptomatic hemorrhage. Patients had a favorable outcome at discharge (mean NIHSS 8.9 ± 8.7) and 6 (50%) had an NIHSS ≤ 4 at discharge.

Conclusions—Multimodal rescue therapy was effective at recanalizing occluded cerebral vessels that failed thrombolysis without an excess risk of ICH. (Stroke. 2005;36:2286-2288.)

Key Words: acute ■ angioplasty ■ endovascular therapy ■ platelet aggregation inhibitors ■ stroke ■ thrombolysis

For large artery occlusions, intraarterial (IA) thrombolysis is more effective than intravenous (IV) thrombolysis, but even with IA thrombolysis, 20% to 40% of vessels will not recanalize.¹ Such single-modality approaches are often inadequate, likely as a result of the heterogeneous nature of ischemic stroke. A multimodal approach combining fibrinolytics, anticoagulants, platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists, and angioplasty and stenting, as used for the treatment of acute coronary syndromes, may also be effective for the treatment of acute ischemic stroke.² We have treated 12 patients with such a combination, and in this report, we present our preliminary results.

Methods

We reviewed our prospectively collected peripheral interventional laboratory database to identify all patients who were treated endovascularly for acute ischemic stroke (IS). All patients were treated with a combination of thrombolytics, GPIIb/IIIa antagonists, angioplasty, stenting, and mechanical thrombectomy. Treatment methods and pharmacologic agent doses were individualized based on vascular anatomy, stroke mechanism, size of infarct on the screening computed tomography or magnetic resonance imaging scan, arterial blood pressure, serum glucose value, patient age, and status and symptom duration, all factors that are correlated with neurologic outcome and the risk of intracranial hemorrhage (ICH).³ Pharmacologic agents were given in aliquots of approximately 25% of the typical coronary or previously reported IA lysis doses up to a maximum of 0.25 mg/kg of abciximab and 25 mg of rtPA (or equivalent dose of reteplase). Atherothrombotic occlusions (suggested by atherosclerosis risk factors, stuttering symptom onset, tapered occlusion, proximal atherosclerosis, or the lack of an obvious cardioembolic source) were treated with standard coronary balloon angioplasty catheters (Maverick; Boston Scientific) and GPIIb/IIIa inhibitors preferentially; whereas snaring was considered in patients with presumed embolic occlusions (suggested by abrupt symptom onset, obvious cardioembolic source, or angiographic appearance consistent with embolism, ie, abrupt vessel cutoff, meniscus sign). Informed consent was obtained from the patient or a legal surrogate. The Institutional Review Board has approved endovascular acute stroke treatment at our institution on a compassionate-use basis and also approved our prospective database.

Results

Twelve patients were treated within 3.8 ± 2.2 hours of stroke onset (Table 1). The mean initial National Institutes of Health Stroke Scale (NIHSS) score was 19.4 ± 4.1 (range, 15 to 27).
The mean dose of IA rtPA given was 17.1 ± 8.6 mg (range, 5 to 30 mg), and the mean dose of reteplase was 2.0 units.

One patient (patient 3) was not given a thrombolytic agent because of stroke duration >6 hours and profound hyperglycemia. Eleven patients received an IV (5), IA (5), or combined IV/IA (one) abciximab bolus (mean dose 11.8 ± 5.8 mg). One patient was treated with 13.8 mg of IV eptifibatide. All patients received heparin (mean dose 3.29 ± 1.484 U).

Eleven patients were treated with angioplasty (Table 2). Five patients received aspirin and clopidogrel. Two patients were treated with stents for a severe underlying stenosis of the internal carotid artery origin. Additionally, a snare was used in 3 patients and a rheolytic thrombectomy device was used to treat one patient.

Technical success was achieved in 11 (91.7%) patients with complete (TIMI III) recanalization in 8 (66.7%) and partial (TIMI II) recanalization in 3 (25%) (Table 2). Ten (83.3%) patients had neurologic improvement before discharge (>4-point decrease of NIHSS), whereas 7 (58%) had a >50% improvement. The mean discharge NIHSS of the 10 patients discharged to home or rehabilitation was 6.7 ± 7.3; 6 of these patients were discharged directly to home with minimal or no residual deficits.

There were 2 complications: one symptomatic (>4-point deterioration on NIHSS) subarachnoid hemorrhage and one asymptomatic (no change in NIHSS) petechial hemorrhage. Two patients died of their strokes.

**Discussion**

Ischemic stroke is a heterogeneous disease, and a single approach to treatment will necessarily fail in certain patients because stroke can be caused by emboli or thrombi of varying platelet and fibrin composition of various ages. A patient-specific approach combining a variety of drugs (fibrinolytics and GPIIb/IIIa antagonists) and mechanical approaches (angioplasty and clot disruption or removal), each chosen based on the likely mechanism of stroke, may increase the chance of recanalization. The combination of a thrombolytic and a GPIIb/IIIa antagonist may have a synergistic effect on recanalization efficiency and may contribute to a good clinical outcome.

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Vessel</th>
<th>NIHSS</th>
<th>Etiology</th>
<th>Symptom Duration (hours)</th>
<th>Post-Operative Stroke</th>
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<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>MCA</td>
<td>18</td>
<td>Stenosis</td>
<td>3</td>
<td>No</td>
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<tr>
<td>2</td>
<td>60</td>
<td>MCA</td>
<td>22</td>
<td>Embolic</td>
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<td>No</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>MCA/ICA</td>
<td>15</td>
<td>Combined</td>
<td>8</td>
<td>No</td>
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<tr>
<td>4</td>
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<td>MCA</td>
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<td>Embolic</td>
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<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>MCA/ACA</td>
<td>15</td>
<td>Embolic</td>
<td>4</td>
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</tr>
<tr>
<td>6</td>
<td>56</td>
<td>MCA/ICA</td>
<td>16</td>
<td>Combined</td>
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<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>MCA/ICA</td>
<td>19</td>
<td>Combined</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>BA</td>
<td>17</td>
<td>Stenosis</td>
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<td>9</td>
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<td>MCA</td>
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<td>Embolic</td>
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</tr>
<tr>
<td>10</td>
<td>79</td>
<td>MCA/ICA</td>
<td>25</td>
<td>Embolic</td>
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</tr>
<tr>
<td>11</td>
<td>83</td>
<td>MCA</td>
<td>22</td>
<td>Embolic</td>
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</tr>
<tr>
<td>12</td>
<td>69</td>
<td>MCA/ICA</td>
<td>27</td>
<td>Embolic</td>
<td>5.9</td>
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</tr>
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</table>

Mean 66.0 19.4 3.8
SD 11.6 4.1 2.2

NIHSS indicates National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ICA, internal carotid artery; ACA, anterior cerebral artery; BA, basilar artery.

The mean dose of IA rtPA given was 17.1 ± 8.6 mg (range, 5 to 30 mg), and the mean dose of reteplase was 2 ± 0.6 units. One patient (patient 3) was not given a thrombolytic agent because of stroke duration >6 hours and profound hyperglycemia. Eleven patients received an IV (5), IA (5), or combined IV/IA (one) abciximab bolus (mean dose 11.8 ± 5.8 mg). One patient was treated with 13.8 mg of IV eptifibatide. All patients received heparin (mean dose 3.292 ± 1.484 U).

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**TABLE 2. Intervention Details and Clinical Outcomes**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pharmacological Intervention</th>
<th>Mechanical Intervention</th>
<th>Recanalization*</th>
<th>Discharge NIHSS</th>
<th>NIHSS Improvement</th>
<th>Asymptomatic ICH</th>
<th>Symptomatic ICH</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IA Lytics, Abciximab</td>
<td>PTA</td>
<td>TIMI 3</td>
<td>3</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>IV tPA, Abciximab</td>
<td>PTA,† Snare</td>
<td>TIMI 3</td>
<td>16</td>
<td>6</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Abciximab</td>
<td>PTA</td>
<td>TIMI 3</td>
<td>0</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>IA Lytics, Abciximab</td>
<td>PTA</td>
<td>TIMI 3</td>
<td>1</td>
<td>14</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>5</td>
<td>IA Lytics, Abciximab</td>
<td>PTA</td>
<td>TIMI 2</td>
<td>11</td>
<td>4</td>
<td>Yes‡</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>IA Lytics, Eptifibatide</td>
<td>PTA, Stent†</td>
<td>TIMI 2</td>
<td>3</td>
<td>13</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>IA Lytics, Abciximab</td>
<td>PTA, Stent, Angiojet</td>
<td>TIMI 2</td>
<td>4</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>IA Lytics, Abciximab</td>
<td>PTA</td>
<td>TIMI 3</td>
<td>1</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>Yes§</td>
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<tr>
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<td>IA Lytics, Abciximab</td>
<td>Wire Manipulation</td>
<td>TIMI 3</td>
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<td>16</td>
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<td>No</td>
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<td>PTA, Snare</td>
<td>TIMI 1 (ACA TIMI 3)</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
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<tr>
<td>11</td>
<td>IA Lytics, Abciximab</td>
<td>PTA</td>
<td>TIMI 3</td>
<td>22</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>IA Lytics, Abciximab</td>
<td>PTA, Snare</td>
<td>TIMI 3</td>
<td>22</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Mean 6.7 12.4
SD 7.3 5.5
Median 3.5 14.5

ICH indicates intracerebral hemorrhage; IA, intra-arterial; IV, intravenous; PTA, angioplasty.

*Modified Thrombolysis in Myocardial Infarction grade (TIMI) 2 or 3.
†Including extracranial internal carotid PTA or stenting.
‡Petechial
§Subarachnoid hemorrhage.
outcome and a lower risk of ICH. Additionally, administering abciximab intraarterially along with angioplasty and stenting may facilitate thrombolysis by increasing thrombolytic penetration into the thrombus and by treating any underlying flow limiting stenosis. Snares and rheolytic devices decrease the clot burden and improve recanalization rates. Our experience with this multimodal approach has shown promising results.

We were able to achieve recanalization in nearly all patients, despite the fact that nearly half of our patients had internal carotid occlusions, which are the most difficult occlusions to recanalize. This recanalization had a clinical benefit because 10 of 12 patients had significant clinical improvement and half were discharged to home either normal or nearly normal neurologically. For comparison, IA thrombolysis in the PROACT-II trial resulted in TIMI 3 flow in only 19% of patients, although carotid terminus occlusions were not included. Importantly, there was a low rate of symptomatic ICH in our patients despite combining thrombolytics, GPIIb/IIIa antagonists, high doses of heparin, and angioplasty. In PROACT-II, symptomatic ICH occurred in 10% of patients receiving thrombolytic therapy. Abciximab may be less prone to cause ICH as compared with standard thrombolytics. Other contributing factors to the low ICH rate may have been the adjustment of pharmacologic drug doses, particularly rtPA, and the type of mechanical intervention based on the presence of known factors that increase the risk of ICH and the likely pathophysiology of the stroke.

 Limitations of this study are the small number of patients, the lack of randomized controls, and the nonstandardized treatment approach; the latter is both a weakness and a strength because we feel that a regimented and standardized approach limits the therapeutic options.

Conclusion
Multimodal treatment for acute ischemic stroke can result in very high recanalization rates and good clinical outcomes without an excessive risk of ICH. This approach allows for the individualization of the treatment for each patient, taking into account the pathophysiology of the stroke as well as patient characteristics that favor one treatment over another. A prospective study of this approach is needed with the aim to assess the value of recanalization as a strategy rather than the efficacy of individual drugs or devices.

Acknowledgments
The authors acknowledge the invaluable assistance of Patricia McMahon, RN, in the management and care of these patients.

References
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Stroke. 2005;36:2286-2288; originally published online September 22, 2005;
doi: 10.1161/01.STR.0000179043.73314.4f

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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