Acute Intravenous–Intra-Arterial Revascularization Therapy for Severe Ischemic Stroke

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Background—Intravenous alteplase for acute ischemic stroke is least efficacious for patients with proximal large-artery occlusions and clinically severe strokes. Intra-arterial therapy has the theoretical advantage of establishing a neurovascular diagnosis and high symptomatic artery patency rate but the disadvantage of requiring extra time and technical expertise. A combination of these two approaches may provide the best chance of improving outcome in severe acute ischemic stroke. We sought to assess the safety and feasibility of this approach.

Methods—This was a prospective, open-label study. Sequential patients arriving to our center within 3 hours of stroke onset who were treated with intravenous alteplase were screened for possible additional intra-arterial therapy using noninvasive neuroimaging. Clinical measures and outcomes were recorded prospectively.

Results—A total of 861 patients with ischemic stroke were admitted to Calgary hospitals during the study period. Eight patients over 21 months underwent a combined intravenous–intra-arterial approach. Six received intra-arterial alteplase and 1 underwent intracranial angioplasty; in a final patient, technical aspects prevented intra-arterial therapy. Early neurovascular and/or neurometabolic imaging identified the location of occlusion and tissue-at-risk (DWI-PWI mismatch) in all 8 patients. Two patients had a poor outcome, 1 patient suffered a significant groin hematoma, and there were no instances of symptomatic intracerebral hemorrhage.

Conclusions—Intravenous followed by intra-arterial therapy is a promising approach to the treatment of severe acute ischemic stroke. Early noninvasive neurovascular and neurometabolic imaging is very helpful in choosing candidates for this type of therapy. On-going monitoring of alteplase-treated patients may allow the opportunity to perform rescue intra-arterial therapy. (Stroke. 2002;33:279-282.)

Key Words: intra-arterial therapy stroke, acute stroke, ischemic tissue plasminogen activator

Stroke thrombolytic therapy with intravenous alteplase may be ineffective for patients with severe ischemic stroke due to large vessel occlusion. Angiographically controlled studies using duteplase (double-chain, recombinant tissue-type plasminogen activator) found that recanalization of large vessel occlusions were uncommon after a 60-minute infusion (8.7% for extracranial carotid, 35.2% for M1-MCA [middle cerebral artery]). Intravenous thrombolysis worked best for MCA branch occlusions (M2-MCA or M3-MCA) with a 53.8% and 65.9% recanalization rate, respectively.1

The Prourokinase in Acute Stroke Trial-2 (PROACT-2), an angiographically controlled trial,2 confirmed that for those patients with proximal M1-MCA stem or proximal M2-MCA occlusions, intra-arterial prourokinase improved the proportion of patients who achieved independence (modified Rankin Scale score <3) at 90 days by an absolute increase of 15%. This correlated with a Thrombolysis in Myocardial Infarction (TIMI) grade ≥2 in the symptomatic artery at 2 hours in 66% of patients in the treatment group. Several case series suggest benefit for selected ischemic stroke patients with intra-arterial therapy.3–6

Because the prognoses for proximal MCA, ICA (internal carotid artery), and basilar artery occlusions are so poor despite intravenous thrombolysis, new approaches are needed. Intravenous followed by intra-arterial alteplase has been previously compared with intra-arterial therapy in a pilot randomized trial—the EMS Bridging study.7 We investigated the safety, feasibility, and method of selecting stroke patients for an aggressive treatment approach with intravenous followed by intra-arterial therapy in an open-label, prospective, uncontrolled study.
Methods

Prospective patients treated with intravenous alteplase at our center were selected for additional intra-arterial thrombolysis based on stroke severity, baseline CT scan appearance, persistent arterial occlusion, large perfusion-diffusion (PWI-DWI) mismatch on 3T magnetic resonance imaging (MRI), and/or clinical and neuroimaging findings to suggest basilar thrombosis (Table 1). We did not establish an a priori NIH Stroke Scale (NIHSS) score or age limitation for inclusion or exclusion from additional intra-arterial therapy. Each patient was assessed by the stroke team and underwent an acute cranial CT scan. All patients were treated with full-dose intravenous alteplase (0.9 mg/kg as a 10% loading bolus injection followed by an infusion over 60 minutes) according to accepted criteria. Patients underwent acute neurovascular imaging with transcranial Doppler (TCD), magnetic resonance angiography (MRA), or both. Baseline NIHSS scores were recorded prospectively by a stroke neurologist or trained stroke nurse. CT scans were obtained on a Toshiba Xpress scanner using 5-mm slice thickness parallel to the infero-orbitomeatal line and scored prospectively using the Alberta Stroke Program Early CT Score (ASPECTS) by the attending stroke neurologist.

MR images were obtained using a 3-Tesla scanner (GE Medical Systems) equipped with high performance (40 mT/m) gradients. The mean scan time was 32.5 minutes (n=4 patients; SD=8.3). Assessment of the anatomic maps, DWI, MRA, and “perfusion” data were undertaken in real time by the attending stroke neurologist and neuroradiologist. Diffusion-perfusion mismatch was assessed qualitatively from the relative mean transit time (mTT) and apparent diffusion co-efficient (ADC) maps. TCD examinations were performed using a portable single-channel 2-MHz system (Multigon 500 mol/L), using a standard acute stroke protocol. Arterial patency was assessed using Thrombolysis in Brain Ischemia (TIBI) criteria.

Prior to initiation of intra-arterial therapy, all patients or their surrogates provided informed consent. Intra-arterial therapy was performed by 1 of 3 neuroradiologists (M.E.H., W.H., W.M.), using a femoral artery approach. Intra-arterial alteplase was reconstituted as directed (1 mg tPA [tissue plasminogen activator] to 1 cc sterile water), further diluted 2:1 with sterile water, and applied at the face of the thrombus, in the thrombus, and distal to the thrombus with a pulse-spray technique, 3 cc per application, using 3-cc syringes. This technique was combined where possible with mechanical thrombus disruption using the microcatheter. No more than an additional 20 mg of alteplase was given intra-arterially. Intravenous heparin was given in a 2000-U bolus at the beginning of the procedure and in a bolus fashion intermittently throughout to a maximum of 500 U/h. No heparin or antiplatelet therapy was administered subsequently for 24 hours. Angioplasty and/or stenting were not prospectively planned but were available as “rescue” procedures. Angiographic recanalization of the symptomatic artery was assessed using TIMI grades.

Each patient had a 24-hour follow-up CT scan and/or MRI. Clinical follow-up was conducted at 24 hours and 90 days by the stroke neurologist and/or stroke nurse specialist. Follow-up examinations were not blinded to baseline presentation or to treatment. Poor outcome was defined as death or a modified Rankin scale (mRS) score ≥3. Adverse events (hemorrhage, angioedema) were specifically recorded.

Results

Over 21 months (February 1999 to October 2000), 8 patients underwent a combined intravenous thrombolysis plus intra-arterial approach. Six patients were treated with intra-arterial tPA, 1 was treated with angioplasty, and technical difficulties in 1 prevented intra-arterial treatment. During the same period, 66 additional patients were treated with intravenous alteplase and 861 patients in the Calgary region were admitted with ischemic stroke. All patients presented with severe disabling ischemic stroke with a median NIHSS score of 18. Patients were young (median age 49, range 41 to 83) and were not diabetic or hypertensive.

Neuroimaging findings are shown in Table 2. Angiographic recanalization was achieved in 6 of 7 patients who underwent an intervention (Table 2). In the eighth patient, extremely tortuous arteries prevented intra-arterial therapy. Two patients required intubation during the procedure, delaying therapy for more than 45 minutes in each case. One had brain stem ischemia and the second had a significant Wernicke’s-type aphasia with agitation.

The median time to symptomatic artery opening was just over 5½ hours (Table 3). Two patients had poor outcomes. Patient 3 suffered a right ICA occlusion had his artery reopened with a good initial recovery. Several days later he suffered a pulmonary embolus and then a fatal contralateral (left) internal carotid artery occlusion due to embolus from a left ventricular thrombus. Patient 4 suffered from bilateral vertebral artery occlusions with minimal basilar artery perfusion from the anterior circulation. After intravenous alteplase he had trickle flow through the right vertebral artery (TIMI 2). Acute transluminal angioplasty was performed on the right vertebral artery. Ultimately he suffered a significant brain stem stroke, leaving him dependent. Four of 6 patients in whom reperfusion was achieved did very well, achieving both functional and good neurological outcomes (NIHSS ≤3) at 90 days (Table 2).

There was no incidence of symptomatic intracerebral hemorrhage or significant extracerebral hemorrhage (0% one-sided 97.5% CI 37%). One patient had a groin hematoma that resolved in 24 hours. One patient developed mild hemi-orolingual angioedema, which responded rapidly to intravenous histamine antagonists.

Discussion

The logic of progressing from intravenous to intra-arterial therapy rests on angiographically controlled intravenous tPA studies suggesting that the rate of recanalization of large vessels such as the basilar artery, ICA, and proximal MCA is low with standard intravenous tPA. In addition, the prognosis for large stroke is poor, neuroprotective strategies have failed to date in humans, and the only approach for reduction
in infarct volume and improvement in outcomes derives from restoration of blood flow. Patients in our series had severe stroke with the median NIHSS = 18, similar to the PROACT-II study and more severe than the NINDS tPA Stroke Study.

Choosing patients for additional intra-arterial therapy after they have already been treated with intravenous therapy may be aided by modern neurovascular and neurometabolic imaging. We used this approach in 7 of 8 patients in our cohort using MRI and/or TCD. All patients had an occlusion confirmed at angiography. This compares to 65% in a previous trial that used only clinical and CT criteria to select patients.

We used the ASPECTS grading system to rate baseline CT scans and the TIBI scoring system to assess baseline TCD examinations. All of our patients had a baseline ASPECTS score ≥ 6 and a low TIBI score in the symptomatic artery. It is likely that including patients with high ASPECTS and low TIBI scores results in an increased chance of identifying patients with tissue-at-risk (DWI–PWI mismatch).

We encountered several practical problems. First was the need for anesthesia to allow safe navigation of the branch artery cerebral vessels. Patient's with Wernicke's aphasia are often agitated and require sedation, because of the inability to comprehend or as a direct neurobehavioral effect of dominant hemisphere posterior temporoparietal ischemia. With brain stem ischemia, airway control may necessitate intubation. Addressing the decision to intubate early may prevent delays.

Second was the inability to establish reperfusion, seen in 2 patients in our series, both of whom suffered large cortical strokes. Abnormal cerebrovascular anatomy due to tortuosity, previous occlusion, or dissection may prevent or delay therapy. Other patients have thrombolysis-resistant thrombus. New thrombolytic agents and/or mechanical approaches may be required.

### TABLE 2. Baseline Characteristics, Outcome, and Neurovascular Imaging

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>NIHSS Onset</th>
<th>Intravenous tPA min</th>
<th>MR Scan Time</th>
<th>Occulted Artery on Angiogram</th>
<th>TIMI Flow After Intra-Arterial Therapy</th>
<th>24 h NIHSS</th>
<th>90 d NIHSS</th>
<th>90 d mRS</th>
<th>Artery Sign on CT Scan</th>
<th>ASPECTS</th>
<th>TCD</th>
<th>DWI/PM</th>
<th>MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>41</td>
<td>24</td>
<td>80</td>
<td>n/a</td>
<td>L M2 &amp; L ICA dissection</td>
<td>1</td>
<td>n/a</td>
<td>3</td>
<td>2</td>
<td>—</td>
<td>9</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>83</td>
<td>10</td>
<td>123</td>
<td>45</td>
<td>L M2</td>
<td>3†‡</td>
<td>13</td>
<td>2</td>
<td>3</td>
<td>—</td>
<td>7</td>
<td>n/a</td>
<td>MTT&lt;DWI</td>
<td>L M2 occlusion/slow flow</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>76</td>
<td>15</td>
<td>129</td>
<td>35</td>
<td>R M1 &amp; R ICA dissection</td>
<td>1</td>
<td>17</td>
<td>42</td>
<td>6</td>
<td>Hyperdense MCA sign</td>
<td>6</td>
<td>R carotid occlusion—TBI 1 at 55 mm</td>
<td>MTT&lt;DWI</td>
<td>R ICA occlusion/slow flow</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>53</td>
<td>20</td>
<td>86</td>
<td>n/a</td>
<td>Bilateral vertebral arteries</td>
<td>2</td>
<td>13</td>
<td>12</td>
<td>4</td>
<td>—</td>
<td>10</td>
<td>Basilar occlusion—TBI 1 at 100 mm</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>43</td>
<td>20</td>
<td>65</td>
<td>26</td>
<td>R M1</td>
<td>1‡‡</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>—</td>
<td>7</td>
<td>R MCA occlusion—TBI 1 at 100 mm</td>
<td>MTT&lt;DWI</td>
<td>R M1 occlusion/slow flow</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>40</td>
<td>16</td>
<td>108</td>
<td>24</td>
<td>R M2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>Hyperdense MCA sign</td>
<td>10</td>
<td>R MCA occlusion—TBI 1 at 100 mm</td>
<td>MTT&lt;DWI</td>
<td>R M2 occlusion/slow flow</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>75</td>
<td>19</td>
<td>129</td>
<td>n/a</td>
<td>L M2</td>
<td>0</td>
<td>n/a</td>
<td>5</td>
<td>3</td>
<td>—</td>
<td>9</td>
<td>R M2 occlusion—TBI 2 at 100 mm</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>45</td>
<td>17</td>
<td>95</td>
<td>n/a†</td>
<td>L M1</td>
<td>0</td>
<td>16</td>
<td>8</td>
<td>3</td>
<td>Hyperdense MCA sign</td>
<td>8</td>
<td>L MCA occlusion—TBI 1 at 100 mm</td>
<td>DWI lesion (no PWI completed)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a, not available; CT, computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; TCD, transcranial Doppler; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; TIBI, Thrombolysis in Brain Ischemia; L, left; R, right; ICA, internal carotid artery; MCA, middle cerebral artery; MTT, mean transit time.

*MR scan time indicates the time in the scanner from the onset of the first image acquisition to the end of the last. This does not include preparation time.

†MRI was performed but abandoned after 2 sequences because of patient agitation and resulting movement artifact.

‡One distal M3 branch remained occluded.
§One M2 branch remained with TIMI 1 flow.

### TABLE 3. Interval Times (min)

<table>
<thead>
<tr>
<th>Event</th>
<th>Median, min (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset-to-door</td>
<td>47.5 (0–100)</td>
</tr>
<tr>
<td>Door-to-intravenous tPA</td>
<td>46.5 (41–84)</td>
</tr>
<tr>
<td>Intravenous tPA bolus-to-first angiogram film</td>
<td>115 (87–190)</td>
</tr>
<tr>
<td>Total on-set-to-first angiogram film</td>
<td>223 (152–313)</td>
</tr>
<tr>
<td>1st angiogram film-to-intra-arterial intervention (n = 7)</td>
<td>87 (38–134)</td>
</tr>
<tr>
<td>Intra-arterial intervention-to-artery open (n = 6)</td>
<td>21.5 (5–60)</td>
</tr>
<tr>
<td>Onset to intravenous tPA</td>
<td>101.5 (65–129)</td>
</tr>
<tr>
<td>Onset to intra-arterial intervention</td>
<td>310 (190–375)</td>
</tr>
<tr>
<td>Total onset-to-artery open time (n = 6)</td>
<td>335 (250–391)</td>
</tr>
</tbody>
</table>

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Third was the slow time-to-treatment. While our door-to-needle times for intravenous alteplase were excellent, approaching a postmarketing standard achieved in Cologne, Germany,1,3 our overall times-to-treatment were longer (median 310 minutes) compared with others (median 210 minutes).2,3 However, in 5 patients we performed MR imaging prior to angiography. Despite actual MR scan times averaging 30 to 35 minutes, the required time is often longer because of pre- and postscan nursing care required for these acutely ill patients. Time saving may be possible by minimizing the number of MR sequences performed.

Despite these problems, among patients who achieved reperfusion, 3 of 6 (50%) did well and 2 of 6 did extremely well (mRS 0 to 1). Ernst et al have recently reported impressive results among a cohort of 20 patients treated with intravenous followed by intra-arterial alteplase, among whom 65% were independent at 90 days. In this cohort, the symptomatic ICH rate was 5% and overall mortality 10%.2,3 Our approach should be distinguished from the EMS Bridging Trial and that of Ernst et al, because our patients received full-dose intravenous tPA. As such, the intra-arterial approach could be considered a “rescue” strategy for failed intravenous thrombolysis.

In summary, we observed no major complications and good outcomes among patients in whom we could establish re-perfusion. Our approach required intensive patient selection efforts using early neurovascular and neurometabolic imaging, immediately after patients had been treated with standard dose (0.9 mg/kg) intravenous alteplase. These results are from a case series and require confirmation. We believe that further investigation of this aggressive interventional management of severe acute ischemic stroke is warranted.

Acknowledgments

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References

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