Safety and Feasibility of Collateral Blood Flow Augmentation After Intravenous Thrombolysis

Derek J. Emery, MD; Peter D. Schellinger, MD; Daniel Selchen, MD; Andre G. Douen, MD; Richard Chan, MD; Ashfaq Shuaib, MD, FRCPC; Kenneth S. Butcher, MD, PhD

Background and Purpose—Collateral flow augmentation using partial aortic occlusion may improve cerebral perfusion in acute stroke. We assessed the safety and feasibility of partial aortic occlusion immediately after intravenous tissue plasminogen activator.

Methods—We conducted an open-label pilot study of partial aortic occlusion after thrombolysis. The primary end point was all serious adverse events within 30 days of treatment.

Results—None of the 22 patients enrolled developed symptomatic parenchymal hemorrhages. Asymptomatic hemorrhagic transformation occurred in 9 patients. Procedure-related adverse events were limited to groin complications (n = 13). Seventy-seven percent of patients experienced neurological improvement (≥4-point improvement of the National Institutes of Health Stroke Scale score).

Conclusions—Partial aortic occlusion as an adjunct to thrombolysis in the treatment of acute stroke appears safe. Studies aimed at determining the efficacy of this therapeutic approach are warranted.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique Identifier: NCT01006993.

Key Words: acute Rx ■ acute stroke ■ cerebral blood flow ■ cerebral hemodynamics ■ thrombolysis ■ thrombolytic Rx

Despite thrombolytic treatment with intravenous tissue plasminogen activator (tPA), up to two thirds of patients are left with functional disability.1 In many cases, this may be related to incomplete recanalization.2 Collateral blood flow through leptomeningeal vessels can preserve tissue at risk in acute ischemic stroke.3 Abdominal aortic luminal restriction has been postulated to increase recruitment of leptomeningeal collateral vessels and in animal models, this results in increased cerebral blood flow and attenuated infarct expansion.4–7

An intravascular catheter capable of restricting the lumen of the abdominal aorta in stroke patients (NeuroFlo) has been developed. Patients who have failed to respond to thrombolysis may be the ideal NeuroFlo candidates, because they likely have persisting perfusion deficits. We aimed to assess the feasibility and safety of partial aortic occlusion after thrombolysis.

Materials and Methods

This study was a multicenter single-arm, open-label, safety and feasibility trial registered with clinicaltrials.gov (registration number: NCT01006993). Acute ischemic stroke patients with persisting neurological deficits after intravenous tPA were eligible. Informed consent was obtained in all cases.

The initial 9 patients underwent perfusion (PWI) and diffusion-weighted MRI (DWI) pre- and postprocedure. Patients were enrolled only if PWI confirmed hypoperfusion. DWI lesion and PWI (Tmax threshold +2s) deficit volumes were measured as previously described.8 The remaining 13 patients were enrolled if they had persisting neurological deficits at the conclusion of the tPA infusion.

An abdominal angiogram was performed and the NeuroFlo device (9 Fr [n = 18] or 7 Fr [n = 4]) catheter with 2 balloons inserted into the aorta through the femoral artery. The balloons were inflated to narrow the aortic lumen approximately 70% for 45 minutes.

Adverse events within 90 days of treatment were adjudicated by an independent Data and Safety Monitoring Board. Hemorrhagic transformation was assessed on 24-hour CT and classified as described previously.9

Results

Twenty-two patients (9 female) with cortical infarcts were enrolled (Table 1). Nine patients developed asymptomatic petechial hemorrhagic infarction within 7 days of treatment. There were no cases of parenchymal hematoma.

Adverse events occurred in 21 patients (serious in 8, including 2 deaths). One death was secondary to infarct progression on Day 8 and the second patient died after cardiopulmonary failure at 44 days.

Received November 4, 2010; accepted November 5, 2010.

From the Department of Radiology (D.J.E.) and the Division of Neurology (A.S., K.B.), University of Alberta, Edmonton, Alberta, Canada; the University of Erlangen (P.D.S.), Erlangen, Germany; Trillium Health Centre (D.S., A.D.), Mississauga, Canada; and the University of Western Ontario (R.C.), London, Canada.

Correspondence to Kenneth S. Butcher, MD, PhD, The University of Alberta, 2E3.27 Walter Mackenzie Centre, 8440-112 Street, Edmonton, Alberta T6G 2B7, Canada. E-mail ken.butcher@ualberta.ca

© 2011 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.607846

1135
The most common procedure-related adverse events were groin hematomas/bleeding (n = 11/0510) and femoral pseudoaneurysms (n = 3). Two groin hematomas were associated with anemia secondary to blood loss. One patient had temporary renal dysfunction secondary to iodinated contrast.

A National Institutes of Health Stroke Scale (NIHSS) score improvement of ≥4 points at 90 days occurred in 17 of 22 patients (77%; Table 2). The median NIHSS score improvement at 90 days was 9.5 (range, 4 to 18). NIHSS score was ≤2 in 8 of 22 (36%) and Rankin score was ≤2 in 9 of 22 (41%) at 90 days.

DWI lesion volumes were stable in 6 of 9 and increased in 3 of 9 patients. PWI demonstrated a decrease in hypoperfused tissue volume in 6 of 9 patients. In 2 patients, improved perfusion occurred despite persisting arterial occlusions (Figure).

Discussion

This study demonstrates the feasibility of combining thrombolysis with partial aortic occlusion. The combination does not appear to be associated with an increased risk of hemorrhage.

All hemorrhagic infarction was asymptomatic and petechial. The rate of hemorrhagic infarction (32%) was comparable to that seen in other thrombolysis trials.1 The risks of this therapeutic approach were related to insertion of the catheter, including groin hematomas and femoral pseudoaneurysms, all of which resolved completely.

Small sample size and lack of a control group in this study preclude any conclusions about treatment efficacy. The lack of vascular and blood flow imaging in all patients makes it impossible to determine if clinical improvement was related to tPA and/or collateral flow augmentation. Nonetheless, a decrease in the volume of hypoperfused tissue can occur despite persisting arterial occlusion (Figure). This perfusion improvement may be due to collateral flow, but a randomized trial with patients stratified by arterial occlusion site will be required to determine if aortic occlusion improves outcome after thrombolysis.

Appendix

Data and Safety Monitoring Board: Dr Irfan Altafullah (Chair), Minneapolis, MN; Dr Anand Vaishnav, Louisville, KY; and Dr Robin Roberts, Hamilton, Ontario, Canada.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Pre-tPA NIHSS, median</td>
</tr>
<tr>
<td>Symptom onset to tPA, h; median</td>
</tr>
<tr>
<td>Symptom onset to aortic occlusion, h; median</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Clinical Outcomes and MRI Data (First 9 Patients Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NIHSS</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>NA</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>17</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; MRA, MR angiography; NA, not available (patient sedated); ICA, internal carotid artery.
Sources of Funding
This study was funded by CoAxia Inc, Maple Grove, MN. K.S.B.
receives salary support awards from the Canadian Institutes for
Health Research, the Heart and Stroke Foundation of Alberta, NWT,
and Nunavut and Alberta Innovates Health Solutions.

Disclosures
None.

References
Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR,
Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G,
Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early
stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS
2. Christou I, Alexandrov AV, Burgin WS, Wojner AW, Felberg RA,
Malkoff M, Grotta JC. Timing of recanalization after tissue plasminogen
activator therapy determined by transcranial Doppler correlates with
3. Liebeskind DS. Aortic occlusion for cerebral ischemia: from theory to
aortic occlusion improves perfusion deficits and infarct size following
6. Hammer M, Jovin T, Wahr JA, Heiss WD. Partial occlusion of the
descending aorta increases cerebral blood flow in a nonstroke porcine
augmentation of cerebral blood flow by intermittent aortic occlusion.
8. Butcher KS, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C,
36:1153–1159.
9. Larrue V, von Kummer RR, Muller A, Bluhmki E. Risk factors for severe
hemorrhagic transformation in ischemic stroke patients treated with recombinant
tissue plasminogen activator: a secondary analysis of the European–Australasian
Safety and Feasibility of Collateral Blood Flow Augmentation After Intravenous Thrombolysis
Derek J. Emery, Peter D. Schellinger, Daniel Selchen, Andre G. Douen, Richard Chan, Ashfaq Shuaib and Kenneth S. Butcher

Stroke. 2011;42:1135-1137; originally published online February 24, 2011;
doi: 10.1161/STROKEAHA.110.607846

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/4/1135

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/