Is Intra-Arterial Thrombolysis Beneficial for M2 Occlusions? Subgroup Analysis of the PROACT-II Trial

Ralph Rahme, MD; Todd A. Abruzzo, MD; Renee’ Hebert Martin, PhD; Thomas A. Tomsick, MD; Andrew J. Ringer, MD; Anthony J. Furlan, MD; Janice A. Carrozzella, RN; Pooja Khatri, MD, MSc

Background and Purpose—The role of endovascular therapy for acute M2 trunk occlusions is debatable. Through a subgroup analysis of Prolyse in Acute Cerebral Thromboembolism-II, we compared outcomes of M2 occlusions in treatment and control arms.

Methods—Solitary M2 occlusions were identified from the Prolyse in Acute Cerebral Thromboembolism-II database. Primary endpoints were successful angiographic reperfusion (TICI 2–3) at 120 minutes and functional independence (mRS 0–2) at 90 days.

Results—Forty-four patients with solitary M2 occlusions, 30 in the treatment arm and 14 in the control arm, were identified. Successful reperfusion (TICI 2–3) was achieved in 53.6% and 16.7% of patients in the treatment and control arms, respectively (P=0.04). A favorable clinical outcome (mRS 0–2) was observed in 53.3% and 28.6%, respectively (P=0.19). Baseline characteristics were similar between the 2 groups.

Conclusions—Intra-arterial thrombolysis may lead to a 3-fold increase in the rate of early reperfusion of solitary M2 occlusions and could potentially double the chance of a favorable functional outcome at 90 days.

Clinical Trial Registration—This trial was not registered because enrollment began before July 1, 2005. (Stroke. 2013;44:XXX-XXX.)

Key Words: acute ischemic stroke • intra-arterial thrombolysis • middle cerebral artery • prourokinase

The benefit of intra-arterial (IA) thrombolysis for acute occlusions of the M2 division of the middle cerebral artery (MCA) remains debatable, with variable rates of angiographic (43%–82%) and clinical (41%–75%) success.1–4 Moreover, it was recently suggested that, given the limited vascular territory, functional outcome could be independent of the revascularization status after IA therapy.5 To answer the question whether IA intervention for M2 occlusions is beneficial and safe, we performed a subgroup analysis of the Prolyse in Acute Cerebral Thromboembolism-II (PROACT-II) trial.

Materials and Methods

PROACT-II was an open-label randomized controlled trial with blinded follow-up conducted in 54 North American centers.6 One hundred eighty adult patients with National Institutes of Health stroke scale ≥2 and angiographically proven M1 or M2 MCA occlusions were randomized in a 2:1 ratio to either 9 mg IA recombinant prourokinase (r-proUK) + low-dose intravenous (IV) heparin (2000 units bolus followed by 500 units/hour infusion × 4 hours) or low-dose IV heparin alone. Mechanical clot disruption was not allowed and treatment had to be started within 6 hours of symptom onset. Reperfusion status was determined on control angiograms 2 hours posttreatment according to thrombolysis in myocardial infarction (TIMI) grading scale.6 Favorable outcome was defined as modified Rankin scale (mRS) ≤2 at 90 days. Head computed tomography was obtained at baseline, 24 hours, and 7 to 10 days after treatment. The main finding was a statistically significant benefit of IA r-proUK both in terms of successful reperfusion (TIMI 2–3) at 120 minutes (66% versus 18%; P<0.001) and favorable clinical outcome at 90 days (40% versus 25%; P=0.04).

For this subgroup analysis, all PROACT-II patients who were treated per protocol and had available imaging were included. Two authors (T.A.T. and P.K.) reviewed angiograms, identified cases where a solitary M2 occlusion was the target lesion, and graded 2-hour reperfusion status using the modified thrombolysis in cerebral infarction (TICI) system.7 Treatment and control groups were compared for the following outcome measures: successful reperfusion (TICI 2–3) at 120 minutes, functional independence (mRS 0–2) at 90 days, intracerebral hemorrhage (ICH), and mortality. Statistical analyses were performed using SAS/STAT software (SAS Institute Inc., Cary, NC, USA). Fisher exact test was used for categorical variables and Student t test for numeric variables. Statistical significance was set at P<0.05.

Results

Of the 180 patients enrolled in PROACT-II, 162 were treated per protocol. Eight had unavailable imaging. The angiograms of the remaining 154 patients, 105 in the treatment arm and 49 in the control arm, were reviewed. Forty-four solitary M2 occlusions, 30 in the treatment arm and 14 in the control arm, were identified. 30 in the treatment arm and 14 in the control arm, were identified. Forty-four patients with solitary M2 occlusions, 30 in the treatment arm and 14 in the control arm, were identified.

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arm, were identified. These were 21 men and 23 women with a mean age of 66.2 years and a mean National Institutes of Health stroke scale of 15.3. The left side was affected in 27 patients (61.4%) and the superior M2 division in 19 patients (43.2%). Patient and stroke characteristics were similar between groups. However, patients in the control arm tended to have more diabetes and ischemic heart disease. Conversely, patients in the treatment arm tended to be older with more frequent involvement of the superior M2 division (Table 1).

Reperfusion status (Table 2) could not be determined for 4 patients with incomplete angiograms, 2 in the treatment group and 2 in the control group. Successful reperfusion (TICI 2–3) at 120 minutes was achieved in 53.6% (15/28) patients in the treatment arm, compared with only 16.7% (2/12) in the control arm (P=0.04). Moreover, the rate of TICI 2B or 3 reperfusion was substantially higher in the treatment arm (50% versus 8.3%; P=0.02). Similarly, there was a trend toward better clinical outcomes (Table 2) in the treatment arm, with 53.3% (16/30) patients achieving functional independence (mRS 0–2) at 90 days, compared with only 28.6% (4/14) patients in the control arm (P=0.19).

Posttreatment ICH (Figure) was observed in 46.7% (14/30) patients in the treatment arm and in 21.4% (3/14) patients in the control arm (P=0.18). However, symptomatic ICH (ie, any ICH with neurological deterioration) occurred only in 2 patients (6.7%) in the treatment arm and none in the control arm (P=1.00). Likewise, mortality rates (Figure) were similar between the 2 groups (26.7% versus 21.4%; P=1.00).

Discussion
In this study, IA r-proUK thrombolysis was associated with a statistically significant, over 3-fold increase in early reperfusion of solitary M2 occlusions, from 16.7% to 53.6%. Likewise, there was a trend toward better clinical outcomes with an almost 2-fold increase in functional independence at 90 days, from 28.6% to 53.3%. Although this difference did not reach statistical significance, its large magnitude despite the small sample size favors underpowered analysis over lack of benefit. More importantly, the benefit of IA thrombolysis did not come at the expense of increased morbidity and mortality. Although ICH was twice as common in the treatment group, only 6.7% of patients experienced symptomatic ICH, which occurred in 2 patients in the treatment group and none in the control group.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IA r-proUK+IV Heparin</th>
<th>IV Heparin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.1±13.5</td>
<td>62.1±15.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Male gender</td>
<td>14/30 (46.7%)</td>
<td>7/14 (50%)</td>
<td>1.00</td>
</tr>
<tr>
<td>White race</td>
<td>25/30 (83.3%)</td>
<td>12/14 (85.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18/30 (60%)</td>
<td>10/14 (71.4%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6/30 (20%)</td>
<td>7/14 (50%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.6±3.6</td>
<td>8.5±5.9</td>
<td>0.54</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3/29 (10.3%)</td>
<td>4/14 (28.6%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7/29 (24.1%)</td>
<td>4/14 (28.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>4/30 (13.3%)</td>
<td>3/14 (21.4%)</td>
<td>0.66</td>
</tr>
<tr>
<td>National Institutes of Health stroke scale</td>
<td>15.4±5.4</td>
<td>15.0±5.0</td>
<td>0.82</td>
</tr>
<tr>
<td>Time to treatment, h</td>
<td>4.9±1.1</td>
<td>5.4±0.6</td>
<td>0.14</td>
</tr>
<tr>
<td>ASPECTS score</td>
<td>7.4±1.8</td>
<td>7.1±1.8</td>
<td>0.60</td>
</tr>
<tr>
<td>Left side</td>
<td>17/30 (56.7%)</td>
<td>10/14 (71.4%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Superior division</td>
<td>16/29 (55.2%)</td>
<td>3/14 (21.4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dominant M2 (&gt;2/3 MCA)</td>
<td>11/29 (37.9%)</td>
<td>4/14 (28.6%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Collateral flow</td>
<td>5/30 (16.7%)</td>
<td>2/14 (13.4%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; mRs, modified Rankin scale; and TICI, thrombolysis in cerebral infarction.

Table 2. Angiographic and Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>TICI 120 minutes</th>
<th>mRS 90 days</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1*</td>
<td>2–3*</td>
<td>0–2A†</td>
<td>2B–3†</td>
<td>0–2‡</td>
<td>3‡</td>
<td>Total</td>
<td>0–2§</td>
</tr>
<tr>
<td>IA r-proUK+IV heparin</td>
<td>13 (46.4%)</td>
<td>15 (53.6%)</td>
<td>14 (50%)</td>
<td>14 (50%)</td>
<td>25/28 (89.3%)</td>
<td>3/28 (10.7%)</td>
<td>28</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>IV heparin</td>
<td>10 (83.3%)</td>
<td>2 (16.7%)</td>
<td>11 (91.7%)</td>
<td>1 (8.3%)</td>
<td>12/12 (100%)</td>
<td>0/12 (0%)</td>
<td>12</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>17</td>
<td>25</td>
<td>15</td>
<td>37</td>
<td>3</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

mRs indicates modified Rankin scale; and TICI, thrombolysis in cerebral infarction.

*P=0.04.
†P=0.02.
‡P=0.54.
§P=0.19.
arm, the rates of symptomatic hemorrhage and death were comparably low in both groups.

The benefit of aggressive IA interventions for acute M2 occlusions remains controversial.1–4 Tomsick et al1 reported revascularization results in the IMS trials, comprising 23 isolated M2 occlusions. Although only 43.5% were recanalized, 69.5% achieved mRS 0–2 at 90 days. Moreover, 76% of incompletely recanalized lesions had good outcome. In a pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI)/Multi-MERCI trials, Shi et al3 reported 82.1% TIMI 2–3 reperfusion among 28 M2 occlusions, but only 40.7% favorable clinical outcome at 3 months.4 Our analysis of the PROACT-II trial has the benefit of concurrent controls and suggests that IA thrombolysis could be beneficial in patients with acute solitary M2 occlusions, particularly those presenting outside the IV thrombolysis window. In contrast, the benefit of IA therapy following IV thrombolysis in these patients remains to be seen. It is hoped that the recently completed IMS-3 randomized controlled trial (http://www.ims3.org/) will help answer this question.6

This post hoc subgroup analysis has limitations. Patient randomization was not stratified by arterial occlusion site. As a result, the treatment and control arms were not perfectly matched. Although none of the differences in baseline characteristics reached statistical significance, a potential effect of confounding variables on outcome cannot be completely excluded. The sample size was relatively small with limited statistical power, and Bonferroni correction for multiple subgroup analyses was not performed. Thus, the findings of this exploratory analysis will require confirmation in a larger-scale study.

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Disclosures
None.

References
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