Intra-arterial TPA for Stroke

Clinical Area: Acute stroke
Keywords: acute stroke; tissue plasminogen activator (TPA); thrombolytic therapy

Study Type: Randomized controlled trial
Study Aim: To test the feasibility, efficacy, and safety of combined intravenous (IV) and local intra-arterial (IA) recombinant tissue plasminogen activator (r-TPA) therapy for stroke within 3 hours of onset of symptoms.

Outcomes
- Primary: NIHSSS score; death
- Secondary: Functional outcomes as assessed by the Barthel Index, Rankin score, and Glasgow Outcome score.

Design
- Number of subjects: 35 patients: 17 in the IV/IA group and 18 in the placebo/IA group.
- Description of study population: Mean age=66 years; male sex=54%; white race=41-56%; hypertension=50%; diabetes=15%; prior stroke=15%; baseline National Institutes of Health Stroke Scale score (NIHSSS) = 9, 18 (25th and 75th percentiles, respectively).
- Inclusion criteria: NIHSSS of >5; upper age limit of 84 years.
- Exclusion criteria: Patients with previous strokes within 6 weeks were excluded as were those with surgery, biopsy, or hemorrhage within the 30 days before randomization.
- Power: The authors acknowledge not using power calculations in selecting the study sample.
- Method of randomization: A stratified, blocked-randomization scheme was used.
- Intervention: Patients in the intervention group received IV r-TPA (0.6mg/kg, 60 mg maximum, 10% of the dose as a bolus over 1 minute and the remainder over 30 minutes) followed by immediate cerebral arteriography and local IA administration of r-TPA through the catheter if a clot in the appropriate arterial distribution was identified. Patients assigned to the placebo group received IV placebo in a similar manner to the intervention patients followed by immediate cerebral arteriography and local IA administration of r-TPA through the catheter.
- Blinding: The investigator and/or neurologist, neuroradiologist, and the patient were blinded to the contents of the IV medication (r-TPA or placebo), but all local IA treatments were with open-label r-TPA.
- Source of outcome data (e.g. patient self-report, doctor report, lab results): Laboratory values; doctor’s report.
- Length of follow-up: 90 days.
- Completeness of follow-up: None.

Validity
- Is the study type appropriate for the questions being asked? Yes.
- Was the study population typical of patients with this disease? Yes.
- Were the treatment/control groups comparable at baseline? There were no statistically significant differences.
- Was the intervention compared to placebo and/or best accepted intervention? Yes.
- Was there compliance with the intervention? Yes.
- Was there equal intensity of observation of study and control subjects? Yes.
- Was the process of observation likely to effect the outcome? No.
- Intention to treat analysis? No.

Conclusions regarding validity of methods:
The study methods appear valid. However, due to the small sample size, it is likely that the study did not have sufficient power to detect significant differences.
**Results**

- Median time from onset of symptoms to IV therapy was 2.6 (2.3, 2.8) hours in the combined treatment group and 2.7 (1.9, 2.9) hours in the placebo/IA groups.
- There was no difference in the median treatment intervals from time of onset to IV treatment (2.6 vs. 2.7 hours), arteriography (3.3 vs. 3.0 hours), or clot lysis (6.3 vs. 5.7 hours) between the IV/IA and placebo/IA groups.

**Clinical Outcomes**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>IV/IA (n=17)</th>
<th>Placebo/IA (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in NIHSSS (baseline to 7 days)</td>
<td>4 (24%)</td>
<td>4 (24%)</td>
<td>1.00</td>
</tr>
<tr>
<td>NIHSSS&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>72 h</td>
<td>11 (5, 28)</td>
<td>6 (3, 13)</td>
<td>0.20</td>
</tr>
<tr>
<td>7 days</td>
<td>7 (3, 15)</td>
<td>4 (3, 12)</td>
<td>0.29</td>
</tr>
<tr>
<td>3 months</td>
<td>5.5 (2, 35)</td>
<td>1 (0, 13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Barthel (median score), 90 days</td>
<td>90 (0, 100)</td>
<td>95 (60, 100)</td>
<td>0.26</td>
</tr>
<tr>
<td>Rankin (median score), 90 days</td>
<td>3 (1, 5)</td>
<td>1.5 (1, 2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Glasgow (median score, 90 days)</td>
<td>2 (1, 5)</td>
<td>1 (1, 2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>5 (29%)</td>
<td>1 (5.5%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<sup>1</sup>Data expressed as n (%) or median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile)

- There was no significant difference in the proportion of patients with a 7-point or greater improvement in the NIHSSS or a score of 0 or 1 at 7 days (24% for both groups). However, the median score at 3 months was higher in the IV/IA group than in placebo patients (5.5 vs. 1.0, p=0.04).
- There were also no significant differences in the 90-day outcomes as measured by the Barthel Index, Rankin Score, or Glasgow Outcome Score (p>0.05).
- There was a higher, non-statistically significant higher mortality rate in the IV/IA group compared to the placebo/IA group (p=0.06). The death in the placebo group was due to renal failure; 2 of the deaths in the intervention group were caused by MIs, the others were from an acute aortic dissection, breast cancer, and cerebral edema.

**Adverse Effects**

- Life-threatening/fatal bleeding complications occurred in 2 patients, both in the IV/IA group.
- Moderate to severe bleeding complications occurred in 2 IV/IA patients and 1 placebo/IA patient.

**Authors’ Conclusions**

This study demonstrates that IV/IA treatment is feasible although it was not associated with improved clinical outcomes.

**Reviewer’s Conclusions**

There is insufficient evidence from this study to conclude that IV/IA treatment results in better clinical outcomes. Furthermore, the IV/IA treatment arm was associated with an increase in mortality and severe/life-threatening adverse effects.