Sonothrombolysis for Acute Ischemic Stroke
Stefano Ricci, MD, FRCP-Ed; Lavinia Dinia, MD; Massimo Del Sette, MD; Gian Paolo Anzola, MD; Tatiana Mazzoli, MD; Silvia Cenciarelli, MD; Carlo Gandolfo, MD

Several studies have consistently demonstrated the capability of ultrasound to enhance the lysis of intra-arterial thrombi in acute ischemic stroke during systemic intravenous thrombolysis with tissue plasminogen activator (tPA), an intervention also called sonothrombolysis.

Material and Methods

Objectives
1. To quantify the potential benefits of sonothrombolysis in acute ischemic stroke.
2. To quantify the potential harms of sonothrombolysis.

Types of Studies
Randomized controlled trials with clear allocation concealment.

Types of Participants
Patients admitted to hospital with acute ischemic stroke.

Types of Interventions
Sonothrombolysis versus intravenous tPA therapy alone or conventional treatment.

Primary Outcomes
Survival free of significant disability at the end of follow-up.

Secondary Outcomes
Case fatality, vessel recanalization, symptomatic and asymptomatic hemorrhagic transformation, and cerebral hemorrhage.

Results
We included 5 studies, with a total of 233 patients randomized. However, not all patients were available for all outcomes: for instance, follow-up at 3 months (death and dependency) was available for 206 patients (88.4%). Three studies used transcranial color-coded duplex, and 2 used transcranial color doppler. The duration of sonothrombolysis varied from 1 to 2 hours. When we considered all the 5 studies, we observed a statistically significant difference for the primary outcome (death or disability at 3 months; 206 patients; odds ratio, 1.00; 95% CI, 0.46–2.16); failure to recanalize was lower in the sonothrombolysis group (230 patients; odds ratio, 0.28; 95% CI, 0.16–0.50); and there was a nonsignificant trend for increasing cerebral hemorrhages (233 patients; odds ratio, 2.35; 95% CI, 0.95–5.80). When including patients only treated with tPA, the results were very similar.

Conclusions
Our results indicate that sonothrombolysis performed in patients with recent onset ischemic stroke with evidence of middle cerebral artery or posterior cerebral artery occlusion produces a significant increase in the recanalization rate (Figure), associated with a nonsignificant increase of hemorrhagic transformation of the cerebral infarction. There was a statistically significant clinical improvement at the 3-month follow-up in terms of death plus disability rate, although with very wide CIs.

Implications for Practice
There is insufficient evidence to establish the effectiveness and safety of sonothrombolysis in routine clinical practice.

Implications for Research
Sonothrombolysis is a promising technique but there is a clear need for a new multicenter randomized trial.

Acknowledgments
We thank Prof Peter Langhorne and the editorial team in Edinburgh for their help.

Disclosures
None.

Reference

Keywords: hemorrhage ■ recanalization ■ sonothrombolysis
### Figure

Failure to recanalize. CI indicates confidence interval.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Odds Ratio M-H Fixed, 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clootbust 2004</td>
<td>34/63</td>
<td>52/63</td>
<td>0.25 [0.11–0.56]</td>
<td>53.3 %</td>
<td></td>
</tr>
<tr>
<td>Eggers 2005</td>
<td>3/8</td>
<td>7/7</td>
<td>0.04 [0.00–1.00]</td>
<td>10.8 %</td>
<td></td>
</tr>
<tr>
<td>Larue 2007</td>
<td>4/8</td>
<td>4/9</td>
<td>1.25 [0.19–8.44]</td>
<td>4.2 %</td>
<td></td>
</tr>
<tr>
<td>Eggers 2008</td>
<td>8/19</td>
<td>14/18</td>
<td>0.21 [0.05–0.87]</td>
<td>18.5 %</td>
<td></td>
</tr>
<tr>
<td>Tucson 2009</td>
<td>10/23</td>
<td>8/12</td>
<td>0.38 [0.09–1.65]</td>
<td>13.2 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>121</strong></td>
<td><strong>109</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.28</strong> [<strong>0.16–0.50</strong>]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 59 (Experimental), 85 (Control)
Heterogeneity: Chi² = 4.16, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 4.33 (P = 0.000015)
Test for subgroup differences: Not applicable
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Stroke. 2013;44:e6-e7; originally published online January 3, 2013; doi: 10.1161/STROKEAHA.111.000043

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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