Low-Dose Versus Standard-Dose Tissue Plasminogen Activator for Intravenous Thrombolysis in Asian Acute Ischemic Stroke Patients

To the Editor:

We read with interest the study by Mori et al regarding their experience with intravenous thrombolysis using low-dose (0.6 mg/kg body weight) intravenous tissue plasminogen activator (IV-tPA) in Japanese patients with acute middle cerebral artery occlusion. The study raises some important issues that are especially relevant to Asian acute ischemic stroke (IS) patients.

Data related to systemic thrombolysis for acute IS for Asians have been scarce, primarily because of the small fraction of patients who receive IV-tPA. This assumes immense relevance because acute IS accounts for at least 3 million deaths annually in developing countries, often occurring during relatively young age when compared to those in developed nations.

Randomized controlled trials on thrombolysis with IV-tPA in Asia have been conducted only with Japanese acute IS patients. The results suggest that the clinical efficacy and safety of low-dose IV-tPA in Japanese acute IS patients is comparable to thrombolysis with standard-dose IV-tPA (0.9 mg/kg body weight) in a predominantly Western population.

Distinctly reduced cost of treatment and anticipated lower rates of thrombolysis-related symptomatic intracranial hemorrhage coupled with the comparable efficacy (in Japanese patients) encouraged many other Asian centers to adopt the low-dose or even variable-dose IV-tPA regimens. The relevant results from various Asian studies are summarized in the Table.

Because of the differences in the ethnicities, baseline stroke severity, outcome measures, and tPA dose regimens, it is difficult to compare the available studies from Asian countries. However, some meaningful conclusions can still be drawn. In general, the functional outcomes were almost similar (to the Japanese studies) when the lower-dose tPA regimens were applied among non-Japanese populations across Asia. Interestingly, when the standard-dose IV-tPA regimen was applied, considerably better functional outcomes were observed without increasing the risk of symptomatic intracranial hemorrhage. We adopted the low-dose IV-tPA regimen at our tertiary center during the initial phase. However, our rates of functional independence barely matched with the Japan Alteplase Clinical Trial.

Table. Various Publications From Asia Regarding Intravenous Thrombolysis for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Publication</th>
<th>Country</th>
<th>N of Cases</th>
<th>tPA Dose, % Patients</th>
<th>Baseline NIHSS Median (Range)</th>
<th>Patients With Favorable Clinical Outcome at 3 Months, %*</th>
<th>Symptomatic Intracranial Hemorrhage, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamaguchi et al 2006</td>
<td>Japan</td>
<td>103</td>
<td>Low (0.6 mg/kg), 100</td>
<td>15 (5–30)</td>
<td>36.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Suwanwela et al 2006</td>
<td>Thailand</td>
<td>34</td>
<td>Low (0.6 mg/kg), 5.9</td>
<td>20 (9–32)</td>
<td>Mean NIHSS score 6.9 at 3 months</td>
<td>5.9</td>
</tr>
<tr>
<td>Yoneda et al 2007</td>
<td>Japan</td>
<td>20</td>
<td>Low (0.6 mg/kg), 100</td>
<td>19 (5–37)</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Padma et al 2007</td>
<td>India</td>
<td>54</td>
<td>Standard (0.9 mg/kg), 100</td>
<td>15.5 (11-22)</td>
<td>Barthel Index ≈95%, 35</td>
<td>0</td>
</tr>
<tr>
<td>Salam et al 2009</td>
<td>India</td>
<td>57</td>
<td>Low (fixed dose ≤50 mg), 98.2</td>
<td>12 (5–21)</td>
<td>mRS ≤2, 51</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher (fixed dose 60 mg), 1.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma et al 2009</td>
<td>Singapore</td>
<td>130</td>
<td>Low (0.6 mg/kg), 36.9</td>
<td>12 (10)§</td>
<td>35</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standard (0.9 mg/kg), 63.1</td>
<td>15 (11)§</td>
<td>59</td>
<td>1.2</td>
</tr>
<tr>
<td>Toyoda et al 2009</td>
<td>Japan</td>
<td>600</td>
<td>Low (0.6 mg/kg), 100</td>
<td>13 (7.3-19)</td>
<td>33.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Mori et al 2010</td>
<td>Japan</td>
<td>58</td>
<td>Low (0.6 mg/kg), 100</td>
<td>12 (5–22)</td>
<td>46.6</td>
<td>0</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

*Favorable outcome defined by mRS score 0–1 unless otherwise specified.
†Symptomatic intracranial hemorrhage defined as intracranial hemorrhage within 36 hours and resulting in a neurological deterioration (increase in NIHSS score by ≥4 points).
‡Major neurological improvement defined as decrease in NIHSS >8 points or NIHSS of 0 points at 24 hours.
§Range is expressed as an interquartile range.
Institute of Neurological Disorders and Stroke\textsuperscript{7} trials. Furthermore, we observed considerably higher rates of symptomatic intracranial hemorrhage. We revised our IV-tPA regimen to the standard dose and observed significantly better functional outcomes (modified Rankin scale score, 0–1 in 59\% cases) with low (1.7\%) rates of symptomatic intracranial hemorrhage. Although difficult to substantiate, we believe that low-dose IV-tPA might cause a delayed recanalization and increase the risk of symptomatic intracranial hemorrhage.\textsuperscript{8} Our multiracial population living in Singapore comprises some of the major Asian ethnicities. Hence, our results, coupled with the reports from Thailand\textsuperscript{9} and India,\textsuperscript{10} show that the Japanese experience could not be extrapolated to all Asian countries, especially when there has never been any comparison between the low-dose and standard-dose IV-tPA.

In conclusion, we reiterate our concern about the widely prevalent practice of variable and low-dose IV-tPA regimes across Asian countries. Rapid improvements in socioeconomic conditions are expected to increase the incidence of ischemic stroke. Therefore, timely establishment of a uniform IV-tPA regimen becomes essential, especially when the rapid improvements in health care facilities and public awareness are expected to increase the rates of thrombolysis in acute IS in Asia. Because a large, randomized, controlled trial does not appear feasible, we propose an Asia-wide IS thrombolysis registry to address the prevailing confusion about the IV-tPA dose.

Disclosures

None.

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Stroke. 2010;41:e545-e546; originally published online July 1, 2010;
doi: 10.1161/STROKEAHA.110.582403
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

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/41/8/e545

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