Standard-Dose Intravenous Tissue-Type Plasminogen Activator for Stroke Is Better Than Low Doses

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Background and Purpose—It remains uncertain whether lower dose intravenous tissue-type plasminogen activator (tPA) for stroke is as effective and safe as the standard dose.

Methods—We analyzed data from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China). Patients who were treated within 4.5 hours after symptom onset were included. These patients were divided into 5 groups according to tPA doses given: <0.5, 0.5 to 0.7, 0.7 to 0.85, 0.85 to 0.95, and ≥0.95 mg/kg. Symptomatic intracranial hemorrhage, mortality, and 90-day outcome assessed by modified Rankin scale were analyzed.

Results—A total of 919 patients were enrolled. Among them, 9 had <0.5 mg/kg, 75 had 0.5 to 0.7 mg/kg, 131 had 0.7 to 0.85 mg/kg, 678 had 0.85 to 0.95 mg/kg, and 26 had ≥0.95 mg/kg. Because of sample sizes, only 0.5 to 0.7, 0.7 to 0.85, and 0.85 to 0.95 mg/kg groups were compared. Median tPA doses were 0.64, 0.79, and 0.90 mg/kg, respectively. After adjustment for the baseline variables, there were no significant differences in mortality (5.41% versus 8.66% versus 7.36%; P=0.695) and symptomatic intracranial hemorrhage (0% versus 3.82% versus 1.46%; P=0.106). The 0.5 to 0.7 mg/kg group had less excellent recovery outcome (modified Rankin scale, 0–1) than 0.85 to 0.95 mg/kg group (41.89% versus 53.83%; odds ratio=0.58; P=0.031) at 90 days. The 0.70 to 0.85 mg/kg group had less functional independence outcome (modified Rankin scale, 0–2) than 0.85 to 0.95 mg/kg group (54.33% versus 64.51%; odds ratio=0.66; P=0.036) at 90 days.

Conclusions—Our study suggests that standard-dose intravenous tPA for stroke had more favorable outcome without increasing the risk of symptomatic intracranial hemorrhage than low-dose tPA. For Asian people, 0.9 mg/kg should be the optimal dose of tPA to treat acute ischemic stroke. (Stroke. 2014;45:2354-2358.)

Key Words: safety ■ stroke ■ thrombolytic therapy

Thrombolysis with intravenous tissue-type plasminogen activator (IV-tPA) remains the only proven effective intravenous treatment for acute ischemic stroke (AIS) within 4.5 hours of onset.1,2 The recommended dose of IV-tPA according to the National Institute of Neurological Disorders and Stroke (NINDS) trial was 0.9 mg/kg (maximum 90 mg).3 This standard-dose of tPA was chosen based on the findings of 2 pilot dose-escalation studies, which only enrolled small numbers of subjects (94 cases) in each dose tier.4,5 There has never been any randomized clinical trial to test different doses of tPA in AIS. Therefore, there is controversy on the optimal dose of tPA. In Asia, many hospitals chose a low-dose or even variable-dose IV-tPA regimens6–9 because of the belief that there is racial differences in blood coagulation–fibrinolysis factors, need to reduce cost of treatment, and desire of lower rate of symptomatic intracranial hemorrhage (SICH). To search for any evidence of such practice, we examined whether lower doses of tPA had comparable efficacy and safety to standard dose in Chinese patients with AIS.

Patients and Methods

Study Population and Design

Data were abstracted from the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China) study. TIMS-China was a national prospective stroke registry of thrombolytic therapy with IV-tPA in patients with AIS.10 A total of 67 major stroke centers participated this stroke registry. The study protocol was approved by the Ethics Committee of Beijing Tiantan Hospital. The registry was regularly monitored independently by the quality monitoring committee of TIMS-China and an independent Research Organization. All patients or patients’ care providers gave written informed consent before thrombolysis, and all patients were followed up for 90 days.

Patients presenting with ischemic stroke who were given intravenous alteplase (Actilyse, Boehringer Ingelheim, Germany) within 4.5 hours after symptom onset and registered in TIMS-China were included in this study. All patients were fully compliant with Actilyse-labeled use except for the time window and tPA dosage. The criteria were almost the same as it was defined in Thrombolysis in Stroke-Monitoring Study (SITS-MOST)11: (1) were between 18 and 80 years of age; (2) had a clinical diagnosis of stroke; (3) had a cerebral tomographic imaging or MRI scan that ruled out hemorrhage; major

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ischemic infarction, or other nonischemic diseases; and (4) had no contraindication for thrombolyis therapy. Patients with severe stroke as it is seen on the baseline cerebral tomographic imaging or with a National Institutes of Health stroke scale (NIHSS) score of >25 were excluded. The eligible patients were divided into 5 groups according to the tPA doses used: <0.5 mg/kg group, 0.5 to 0.7 mg/kg group, 0.7 to 0.85 mg/kg group, 0.85 to 0.95 mg/kg group, and ≥0.95 mg/kg group.

Outcome Measurements
Main safety and efficacy outcome measurements in this study were SICH assessed by cerebral tomographic imaging or MRI and NIHSS scores at 24 to 36 hours after thrombolysis therapy, mortality at 7 days and 90 days, and the modified Rankin scale (mRS) assessed at 7 days and 90 days.

SICH was defined as (1) per SITS-MOST,11 a type 2 intracranial hemorrhage (blood clot >30% of the infarct area, with substantial space occupation) on the 24 to 36 hours follow-up imaging scan after the treatment, combined with a neurological deterioration of >4 points on the NIHSS from the baseline or the lowest NIHSS score between the baseline and 24 hours after thrombolysis or death; (2) per original NINDS study,1 a hemorrhage that was not seen on a previous cerebral tomographic scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status; (3) per European Cooperative Acute Stroke Study (ECASS) II study,12 any intracranial bleeding, with >4 points worsening on NIHSS score.

The mRS score was assessed by face-to-face follow-up visit in the clinic or a telephone interview with the patient or patient’s care provider. Functional independence was defined as a mRS score of 0 to 2. Excellent recovery was defined as a mRS score of 0 to 1.

Statistical Analysis
The χ² test was used to compare the proportions for categorical variables. The Mann–Whitney U test was used to compare medians for continuous variables. The odds ratio (OR) with its 95% confidence intervals and the adjusted OR with its 95% confidence intervals were analyzed by univariable and multivariable logistic regression on the efficacy and safety outcomes between different dose groups.

All significant baseline variables in the univariable analysis were included in the multivariable model for calculating adjusted OR. A 2-tailed P<0.05 was considered to be statistically significant. All analyses were performed with SAS software version 9.1.3 (SAS Institute Inc, Cary, NC).

Results
Between May, 2007, and April, 2012, a total of 1440 patients who received IV-tPA were registered in the TIMS-china. After excluding the cases with missing data (ie, unclear time of symptom onset, time of thrombolysis, or the doses of tPA, treatment outside of 0- to 4.5-hour window, and violated inclusion), 919 patients were included in the current study. These eligible patients were divided into 5 groups according to the doses of tPA given. There were 9 patients in the <0.5 mg/kg group, 75 in the 0.5 to 0.7 mg/kg group, 131 in the 0.7 to 0.85 mg/kg group, 678 in the 0.85 to 0.95 mg/kg group, and 26 in the ≥0.95 mg/kg group (Figure 1).

Considering the sample size and the incidence of study end point, we only compared 0.5 to 0.7, 0.7 to 0.85, and 0.85 to 0.95 mg/kg groups. The baseline characteristics of the these patients were listed in Table 1.

Figure 1. Study flow chart and numbers of eligible patients in each group. r-tPA indicates recombinant tissue-type plasminogen activator; and TIMS-China, Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China.
Stroke August 2014

Table 1. Baseline Variables of Patients Receiving Different Dose tPA

<table>
<thead>
<tr>
<th>Variables</th>
<th>0.5 to 0.7 mg/kg Group (n=75)</th>
<th>0.7 to 0.85 mg/kg Group (n=131)</th>
<th>0.85 to 0.95 mg/kg Group (n=678)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median tPA dose, mg/kg</td>
<td>0.64 (0.60–0.66)</td>
<td>0.79 (0.76–0.83)</td>
<td>0.90 (0.90–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median age, y</td>
<td>62 (52–71)</td>
<td>68 (57–73)</td>
<td>63 (55–72)</td>
<td>0.074</td>
</tr>
<tr>
<td>Sex male, %</td>
<td>61/75 (81.3)</td>
<td>74/131 (56.5)</td>
<td>422/676 (62.2)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independence (mRS, 0–2)</td>
<td>73/75 (97.33)</td>
<td>126/131 (96.18)</td>
<td>669/676 (98.96)</td>
<td>0.0487</td>
</tr>
<tr>
<td>before stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13/75 (17.33)</td>
<td>23/131 (17.56)</td>
<td>118/678 (17.40)</td>
<td>0.9989</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48/75 (64.00)</td>
<td>80/131 (61.07)</td>
<td>385/678 (56.78)</td>
<td>0.3631</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12/75 (16.00)</td>
<td>25/131 (19.08)</td>
<td>93/678 (13.72)</td>
<td>0.2684</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10/75 (13.33)</td>
<td>7/131 (5.34)</td>
<td>37/678 (5.46)</td>
<td>0.024</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>14/75 (18.67)</td>
<td>21/131 (16.03)</td>
<td>90/678 (13.27)</td>
<td>0.3552</td>
</tr>
<tr>
<td>Median blood glucose, mmol/L</td>
<td>6.80 (5.80–8.15)</td>
<td>6.93 (5.82–8.40)</td>
<td>6.56 (5.90–9.02)</td>
<td>0.8799</td>
</tr>
<tr>
<td>Receiving antiplatelet drug in 24 h before thrombolysis, %</td>
<td>11/75 (14.67)</td>
<td>25/131 (19.08)</td>
<td>83/678 (12.24)</td>
<td>0.1047</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>154 (140–170)</td>
<td>145 (130–160)</td>
<td>147 (131–160)</td>
<td>0.0638</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>86 (80–93)</td>
<td>85 (78–93)</td>
<td>87 (80–100)</td>
<td>0.3919</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>10 (7–17)</td>
<td>10 (6–15)</td>
<td>11 (7–15)</td>
<td>0.941</td>
</tr>
<tr>
<td>Median stroke onset to treatment time (IQR), h</td>
<td>2.92 (2.53–3.18)</td>
<td>2.93 (2.33–3.33)</td>
<td>2.79 (2.33–3.25)</td>
<td>0.2518</td>
</tr>
<tr>
<td>Stroke subtype, %</td>
<td></td>
<td></td>
<td></td>
<td>0.1861</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>43/75 (57.33)</td>
<td>69/129 (53.49)</td>
<td>355/672 (52.83)</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>14/75 (18.67)</td>
<td>12/129 (9.30)</td>
<td>73/672 (10.86)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>12/75 (16.00)</td>
<td>27/129 (20.93)</td>
<td>126/672 (18.75)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>6/75 (8.00)</td>
<td>21/129 (16.28)</td>
<td>118/672 (17.56)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) for continuous and ordinal variables, and number of patients/total number from whom data were available (%) for categorical variables. IQR indicates interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

tPA doses were 0.90 mg, 0.79 mg, and 0.64 mg, respectively; median stroke onset to treatment time was 2.79, 2.86, and 2.90 hours (P=0.941); median NIHSS score were 11, 10, and 10 (P=0.252).

The safety and efficiency outcomes are summarized in Tables 2 and 3. The mRS score at 90 days of different groups was compared in Figure 2. After adjusting for all significant baseline variables in the univariable analysis, there was no significant difference in the rate of SICH between 0.5 to 0.7 and 0.85 to 0.95 group. But interestingly, SICH in 0.7 to 0.85 group was even >0.85 to 0.95 group. When SICH was evaluated by ECASS II definition, the difference was significant (OR=2.92; P=0.006). There was no difference in mortality at either day 7 day or 90 visit. For excellent recovery (mRS, 0–1) at 90 days, 0.5 to 0.7 mg/kg group did significantly worse than that in the 0.85 to 0.95 mg/kg group (OR=0.58; P=0.031).

Table 2. Main Safety and Functional Outcomes of Patients Received 0.5 to 0.7 mg/kg and 0.85 to 0.95 mg/kg tPA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0.5 to 0.7 mg/kg Group n/N (%)</th>
<th>0.85 to 0.95 mg/kg Group n/N (%)</th>
<th>Unadjusted Analysis</th>
<th>Adjusted Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH (per SITS-MOST)</td>
<td>0/75 (0)</td>
<td>11/678 (1.62)</td>
<td>...</td>
<td>0.972</td>
</tr>
<tr>
<td>SICH (per ECASS II)</td>
<td>0/75 (0)</td>
<td>21/678 (3.10)</td>
<td>...</td>
<td>0.975</td>
</tr>
<tr>
<td>SICH (per NINDS)</td>
<td>0/75 (0)</td>
<td>33/678 (4.87)</td>
<td>...</td>
<td>0.970</td>
</tr>
<tr>
<td>Mortality at 7 d</td>
<td>1/75 (1.33)</td>
<td>27/677 (3.99)</td>
<td>0.72 (0.25–2.05)</td>
<td>0.274</td>
</tr>
<tr>
<td>Mortality at 3 mo</td>
<td>14/74 (5.41)</td>
<td>49/666 (7.36)</td>
<td>0.33 (0.04–2.42)</td>
<td>0.539</td>
</tr>
<tr>
<td>mRS 0–2 at 3 mo</td>
<td>42/74 (56.76)</td>
<td>429/665 (64.51)</td>
<td>0.73 (0.45–1.18)</td>
<td>0.195</td>
</tr>
<tr>
<td>mRS 0–1 at 3 mo</td>
<td>31/74 (41.89)</td>
<td>358/665 (53.83)</td>
<td>0.62 (0.38–1.01)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin scale; NINDS, National Institute of Neurological Disorders and Stroke; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study; and tPA, tissue-type plasminogen activator.

*Adjusted for sex, history of hyperlipidemia, and independent status before the stroke.
†Odds ratios were calculated by comparing the 0.5 to 0.7 mg/kg group with 0.85 to 0.95 mg/kg group.
Our study demonstrated 2 important facts regarding IV-tPA dosages. First, the standard-dose IV-tPA treatment protocol was safe for Chinese patients with stroke, without any increased rate of SICH or mortality compared with the low-dose group. Second, patients with stroke receiving standard-dose IV-tPA may have more favorable outcome than those receiving low doses of IV-tPA.

The efficacy of different doses of IV-tPA has never been formally tested in a randomized and controlled trial. In dose-ranging studies conducted by the NINDS investigators, various doses were tested in small cohorts. Safety analysis demonstrated that SICH seldom occurred in doses of ≤0.85 mg/kg.3,4 The NINDS trial, ECASS III trial, and the meta-analysis of them had provided strong evidence for the overall net benefit of standard-dose IV-tPA (0.9 mg/kg, max 90 mg/kg) in AIS within 4.5 hours after symptom onset.1,2,13 In ECASS, a high dose (1.1 mg/kg) of tPA was tested for AIS within 6 hours from the onset of symptoms, but the occurrence of large parenchymal hemorrhages in the tPA-treated group was significantly more frequent than placebo group.14 Interestingly, there has never been any randomized clinical trial testing low-dose tPA therapy in AIS. A proposed trial to compare 0.6 to 0.9 mg/kg of tPA was not approved for funding by NINDS.

Racial differences may have had an impact on the safety and efficacy of tPA therapy in AIS. It has been postulated that Asian population had higher rates of tPA-related intracranial hemorrhage because of the racial differences in blood coagulation–fibrinolysis factors, such as in the altered functions of fibrinogen and factor XII.15 And Asians also had higher prevalence of intracranial atherosclerotic diseases. Encouraged by the Japan Alteplase Clinical Trial (J-ACT), which showed that low-dose IV-tPA regimen (0.6 mg kg) in Japanese patients with AIS provided benefits comparable to the standard dose that was used in patients in the NINDS trial,16 many Asian centers adopted the low-dose or even variable-dose IV-tPA regimen. However, J-ACT was only a single-arm observational study. The comparison was between 2 different ethnic populations, and the differences of baseline variables were not adjusted.

Several case series in various Asian populations directly comparing the effect of dose differences on the safety and efficacy have been reported.7,17–20 The sample sizes of these studies were small, and usually only one low-dose regimen was compared with the standard dose. The results of these studies were often contradictory. Most of them concluded that the standard dose had similar SICH rate to the low-dose regimen. However, the standard dose showed a nonsignificant trend toward better functional outcomes.7,8,17–21
Our study was the largest study of non-Japanese Asian patients receiving different doses of IV-tPA. Three dose regimens were compared. For the 0.85 to 0.95 mg/kg group, it was regarded as the standard-dose tPA (0.9 mg/kg) group because most of patients in this group received 0.90 mg/kg tPA including median, inter-quartile range, and mean dose. For the 0.5 to 0.7 mg/kg group, it was regarded as the dose close to 0.6 mg/kg group.

In our study, all patients were ethnic Chinese Han population, and the difference of baseline variables was adjusted. Similar to previous studies, our study also showed that the standard dose did not produce significant higher rate of SICH compared with low-dose tPA. But for outcome, the standard dose group was significantly better than both low-dose groups, although lower dose may be related with relatively low bleeding risk. In fact, there were no SICH in the lowest dose group of our study. But for standard-dose group, SICH is also infrequent. However, lower dose lowered the chance of revascularization.

Our study had several limitations. This was an observational retrospective study, and therefore, it was not randomized and the sample size was unequal. The dose of each group was in a dose interval, rather than a specified dose, especially for the 0.5 to 0.7 mg/kg and 0.7 to 0.85 mg/kg groups. The selection of different doses was completely determined by the treating physician or the institution and not standardized. These factors were not be statistically adjusted.

Conclusions
In conclusion, our study suggests that Chinese patients with AIS receiving standard-dose IV-tPA had more favorable outcome without increasing the risk of SICH than those receiving low doses of IV-tPA. Our registry provides no justification for using standard-dose tPA (0.9 mg/kg) group because most of patients receiving different doses of IV-tPA. Three dose regimens were not be statistically adjusted.

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Disclosures
None.

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