Baseline National Institutes of Health Stroke Scale–Adjusted Time Window for Intravenous Tissue-Type Plasminogen Activator in Acute Ischemic Stroke

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Background and Purpose—The effect of tissue-type plasminogen activator on functional outcome decreases progressively over time. However, given the differential pattern of arterial occlusion, stroke severity, and speed of ischemic lesion growth among candidates for reperfusion, the time window should be adjusted accordingly. We aimed to identify the impact of time-to-treatment according to stroke severity on functional outcome in patients with acute ischemic stroke.

Methods—We included 581 consecutive patients treated with alteplase according to the European Summary of Product Characteristics criteria. Patients were categorized according to National Institutes of Health Stroke Scale (NIHSS) severity in mild NIHSS (≤8), moderate NIHSS (9–15), and severe stroke NIHSS (≥16). We sequentially analyzed time-to-treatment to achieve favorable outcome (modified Rankin Scale ≤2 at 3 months).

Results—Overall, 19.8% had mild, 30.3% had moderate, and 49.9% had severe stroke. Favorable outcome occurred in 79.1%, 60.8%, and 26.2%, respectively. In patients with mild stroke, younger age (odds ratio [OR], 0.88; 95% confidence intervals [CI], 0.8–0.95), no previous history of stroke (OR, 0.16; 95% CI [0.039–0.65]), and no proximal occlusion (OR, 0.183; 95% CI [0.038–0.89]) independently predicted favorable outcome. In patients with moderate stroke, age (OR, 0.95; 95% CI [0.92–0.98]), no proximal occlusion (OR, 0.362; 95% CI [0.17–0.75]), and time-to-treatment before 120 minutes (OR, 2.70; 95% CI [1.14–6.38]) emerged as independent predictors of favorable outcome. In patients with severe stroke, younger age (OR, 0.96; 95% CI [0.94–0.99]), lower previous modified Rankin Scale (OR, 0.42; 95% CI [0.21–0.82]), and absence of proximal occlusion (OR, 0.48; 95% CI [0.25–0.94]) appeared as independent predictors.

Conclusions—The impact of time-to-treatment on favorable outcome varies widely depending on baseline stroke severity. The window for favorable outcome was ≤120 min for moderate strokes. However, time-to-treatment seemed unrelated to functional outcome in mild and severe stroke. (Stroke. 2014;45:1059-1063.)

Key Words: stroke ■ thrombolytic therapy ■ time-to-treatment ■ tissue-type plasminogen activator

Stroke is one of the leading causes of death and a major cause of disability in adults. Since 2008, thrombolysis treatment with alteplase (tissue-type plasminogen activator [tPA]) <4.5 hour in acute stroke has been the only approved treatment and is associated with improved outcome in acute ischemic stroke. Initially, studies as National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study (ECASS) I and II have demonstrated the safety of intravenous thrombolysis during the first 3 hours since stroke symptoms onset. Moreover, meta-analysis of randomized controlled trials, including the ECASS III trial have shown decreasing benefit over time. Although safety and functional outcomes are less favorable beyond 3 hours, the wider time window until 4.5 hours also offers an opportunity from some patients.

Several factors have been shown to be outcome predictors after thrombolysis including baseline stroke severity age, diabetes mellitus, location of intracranial artery occlusion and extend changes on baseline CT scan. Although the beneficial effect of IV tPA decreases progressively over time, the effects of time-to-treatment on short- and long-term outcome may vary widely depending on baseline stroke severity. Therefore, baseline National Institutes of Health Stroke Scale (NIHSS) score adjustment would further refine the influence of time-to-treatment on stroke outcome.

Therefore, we aimed to investigate the impact of the time-to-treatment according to stroke severity on functional outcome in patients with acute ischemic stroke.

Subjects and Methods

Study Population
We prospectively evaluated consecutive patients with acute ischemic stroke treated with IV tPA from March 2001 to September 2012. Of a
total of 794 patients, we excluded those who underwent endovascular treatment (n=154) and those with initial modified Rankin Scale (mRS) ≥3 (n=59). Finally, 581 consecutive patients evaluated and treated according to the criteria of the European Summary of Product Characteristics for tPA treatment until 4.5 hours were included in the analysis.

Clinical Assessment
Clinical demographic data were prospectively collected from our database. All patients underwent a standard neurological examination, electrocardiography, blood pressure, and serum glucose levels at admission. Time-to-treatment, defined as time from symptoms onset to tPA bolus, was recorded.

Stroke severity at baseline was assessed with the NIHSS score by certified neurologist. Patients were categorized according to the stroke severity into 3 groups: mild stroke, when the NIHSS score was ≤8 (n=114 patients); moderate stroke when the NIHSS score was from 9 to 15 (n=162); and severe stroke when the NIHSS score was ≥16 (n=238). Thrichotomy of the NIHSS score in mild (≤8 points), moderate (9–15 points), and severe (≥16 points) was based on the sliding thirctomy approach for the adjustment of outcomes according to baseline stroke severity. All the investigators involved in the clinical assessment were certificated by the National Stroke Association for the use of the NIHSS.

Functional outcome was evaluated at 3 months by the mRS score. Favorable outcome was defined as mRS ≤2.

Transcranial Doppler Ultrasound Protocol
All patients underwent a transcranial Doppler (TCD) to assess the site of vessel occlusion. All the TCD studies were performed by an attending stroke neurologist with extensive experience and certified on TCD in acute stroke, all of whom have considerable experience in performing sonographic studies.

A standard set of diagnostic criteria was applied to diagnose arterial occlusion. Proximal medium cerebral artery (MCA) occlusion was defined as the absence of flow or the presence of minimal flow signal throughout the MCA at an insonation depth between 45 and 65 mm accompanied by flow diversion in the ipsilateral anterior cerebral artery and posterior cerebral artery, according to the Thrombolyis In Brain Ischemia grading system. Distal MCA occlusion was defined as blunted or dampened signals (Thrombolyis In Brain Ischemia 2 or 3) in the symptomatic artery with ≤50% flow than the contralateral MCA and flow diversion signs in ipsilateral neighboring arteries. These patterns of occlusion and recanalization on TCD have shown sensitivity and specificity values of >90% against conventional angiography. Location of basilar artery occlusion and residual flow signals were determined by the presence of abnormal flow signals also using the Thrombolyis In Brain Ischemia grading systems.

Recanalization was assessed 1 hour after tPA bolus by TCD. Partial recanalization on TCD was diagnosed when blunted or dampened signals appeared in a previously demonstrated absent or minimal flow. If velocity improved to normal or elevated values (normal or stenotic signals), complete recanalization was diagnosed.

CT Scan Protocol
On admission, patients underwent a CT scan within the first 4.5 hours after stroke onset. CT scans were assessed for the presence of early parenchymal ischemic changes (to rule out lesions more than one third of the MCA territory) and the hyperdense MCA or internal carotid artery sign. At 24 hours, a control CT was performed to rule out hemorrhagic transformation.

Statistical Analysis
Descriptive and frequency statistical analyses were obtained using IBM SPSS version 17.0 software. The categorical variables are presented as absolute values and percentages, and the continuous variables are presented as mean±standard deviation if normally distributed or median [interquartile intervals] if not normally distributed.

Statistical significance for intergroup differences was assessed by Pearson χ² or Fisher exact test for categorical variables and by Student t or Mann–Whitney U test for continuous variables. Receiver-operating characteristic (ROC) curves were configured to establish different cutoff points of each continuous variable that optimally predicted favorable outcome.

The influence of time-to-treatment was evaluated by sequential analysis every 30 minutes from stroke onset, defining different groups: time-to-treatment 30, time-to-treatment 60, time-to-treatment 90, and so on. ROC curves were also configured to establish the sensitivity and specificity of each time-to-treatment on long-term outcome.

Multivariable logistic regression analyses were performed for each group to determine factors that could be considered as independent predictors of favorable outcome.

Variables showing P<0.1 in univariate analysis were included in the multivariate model. A probability value of <0.05 was considered significant for all tests.

Results
The main baseline characteristics of the series are summarized in Table 1. A total of 581 patients were included. Mean age of the series was 72.30±12.34 years, and 284 patients (48.9%) were women. Median baseline NIHSS score was 15 [range 10–20]. According to stroke severity, the groups were categorized as 115 (19.8%) patients with mild stroke, 176 (30.3%) patients with moderate stroke, and 290 (49.9%) patients with severe stroke. Proximal arterial occlusion (T and proximal MCA occlusion) was seen in 291 (53.5%) and distal in 196 (36%) patients. Mean time from symptoms to IV tPA was 168.79±47.32 minutes. A good outcome at 3 months was achieved in 274 patients (47.2%).

The number of patients treated per time interval from stroke onset were 2, 11, 61, 101, 110, 104, 67, 47, 44, and 33 patients in 0 to 30, 31 to 60, 61 to 90, 91 to 120, 121 to 150, 151 to 180, 181 to 210, 211 to 240, 241 to 270, and >270 minutes groups, respectively. Although time-to-treatment of the series did not predict favorable outcome in the entire cohort (P=0.507), after sequential analysis every 30 minutes from onset, time-to-treatment ≤120 was significantly associated with favorable outcome (P=0.040) with sensitivity 61% and specificity 72%.

The following variables were associated with favorable outcome: younger age (P<0.001), lower previous mRS (P<0.001), female sex (P=0.056), no history of hypertension (P=0.024) or diabetes mellitus (P=0.079), lack of atrial fibrillation (P=0.001), absence of old ischemic lesions or earlier changes on baseline CT scan (P=0.039 and P=0.002, respectively), distal occlusion on TCD (P=0.001) and absence of T occlusion (P<0.001). From all those variables, in the logistic regression model, previous mRS 0 to 1 (OR, 0.59; 95% CI [0.41–0.84]; P=0.004), younger age (OR, 0.95; 95% CI [0.93–0.96]; P<0.001), absence of proximal occlusion (OR, 0.18; 95% CI [0.121–0.273]; P<0.001), and time-to-treatment before 120 minutes (OR, 1.575; 95% CI [1.02–2.43]; P=0.040) emerged as independent predictors of good outcome of the global series.

Mild Stroke
From one hundred and fifteen patients with mild stroke, 40% were women, with a mean age 68.12±13.33 years. NIHSS score on admission was 6 [5–8] points and the time-to-treatment was 171.98±88 minutes. At 3 months, 79.1%
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of patients achieved a good clinical outcome. Proximal occlusion was observed in 16 (15%) patients, distal in 67 (63.2%), and in 13 (12.3%) patients the baseline TCD was normal; 68.8%, 86.6%, and 84.6% of patients with proximal, distal, and normal TCD, respectively, achieved a good clinical outcome.

Among patients with mild stroke time-to-treatment did not predict favorable outcome \( (P=0.895) \), even after the sequential analysis every 30-minute from symptom onset. Variables associated with a good outcome in mild strokes are shown in Table 2. Younger age \( (P<0.001) \), better previous mRS \( (P=0.002) \), no history of stroke \( (P=0.012) \), absence

Table 1. Baseline Clinical Characteristics and Potential Baseline Factors Associated With Favorable or Unfavorable Outcome in All Patients With Stroke

<table>
<thead>
<tr>
<th></th>
<th>Unfavorable Outcome ( (n=307) )</th>
<th>Favorable Outcome ( (n=274) )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75.91±10.69</td>
<td>68.25±12.83</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>162 (52.8)</td>
<td>122 (44.5)</td>
<td>0.056</td>
</tr>
<tr>
<td>Hypertension</td>
<td>211 (69.2)</td>
<td>161 (59.2)</td>
<td>0.024</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>82 (26.8)</td>
<td>56 (20.4)</td>
<td>0.079</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>116 (38.2)</td>
<td>70 (25.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Old CT lesions</td>
<td>50 (16.7)</td>
<td>29 (10.7)</td>
<td>0.039</td>
</tr>
<tr>
<td>Earlier parenchymal changes</td>
<td>64 (26.3)</td>
<td>30 (14.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Proximal occlusion</td>
<td>194 (69.8)</td>
<td>97 (36.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>T occlusion</td>
<td>46 (18.5)</td>
<td>8 (3.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>18 [14–21]</td>
<td>11 [8–16]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-to-treatment, min</td>
<td>170.69±72.52</td>
<td>166.32±66.41</td>
<td>0.507</td>
</tr>
<tr>
<td>Time-to-treatment ≤120</td>
<td>82 (26.7)</td>
<td>93 (34.1)</td>
<td>0.057*</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>86 (29.2)</td>
<td>55 (20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SICH</td>
<td>32 (10.8)</td>
<td>5 (1.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as n (%), mean±SD, or median [interquartile interval]. Variables included in the multivariable model \( (P<0.1) \). CT indicates computerized tomography; NIHSS, National Institutes of Health Stroke Scale; and SICH, symptomatic intracranial hemorrhage.

*Independent predictor of favorable outcome in multivariate analysis.

Table 2. Baseline Clinical Characteristics and Potential Baseline Factors Associated With Favorable or Unfavorable Outcome in Patients With Mild, Moderate, and Severe Stroke

<table>
<thead>
<tr>
<th></th>
<th>Unfavorable Outcome ( (n=24) )</th>
<th>Favorable Outcome ( (n=91) )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77±8.9</td>
<td>65.78±13.34</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>13 (54.2)</td>
<td>33 (36.3)</td>
<td>0.159</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (75)</td>
<td>48 (53.9)</td>
<td>0.101</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (33.3)</td>
<td>15 (16.5)</td>
<td>0.086</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (25)</td>
<td>19 (20.9)</td>
<td>0.781</td>
</tr>
<tr>
<td>Old CT lesions</td>
<td>6 (25)</td>
<td>9 (9.9)</td>
<td>0.082</td>
</tr>
<tr>
<td>Earlier parenchymal changes</td>
<td>2 (9.1)</td>
<td>8 (11.3)</td>
<td>0.775</td>
</tr>
<tr>
<td>Proximal occlusion</td>
<td>5 (26.3)</td>
<td>12 (12.6)</td>
<td>0.043*</td>
</tr>
<tr>
<td>T occlusion</td>
<td>1 (4.8)</td>
<td>0 (0)</td>
<td>0.198*</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>7 [6–8]</td>
<td>6 [5–8]</td>
<td>0.112</td>
</tr>
<tr>
<td>Time-to-treatment, min</td>
<td>174.13±79.47</td>
<td>171.42±91.21</td>
<td>0.895</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>4 (19)</td>
<td>13 (14.3)</td>
<td>0.058</td>
</tr>
<tr>
<td>SICH</td>
<td>3 (14.3)</td>
<td>1 (1.1)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as n (%), mean±SD, or median [interquartile interval]. Variables included in the multivariable model \( (P<0.1) \). CT indicates computerized tomography; NIHSS, National Institutes of Health Stroke Scale; and SICH, symptomatic intracranial hemorrhage.

*Independent predictor of favorable outcome in multivariate analysis.
of old lesions in baseline CT scan ($P=0.082$), and no proximal occlusion ($P=0.043$) were significantly associated with favorable outcome. After adjusting for representative variables (age, mRS previous, history of stroke, presence of old lesions in baseline CT, and proximal occlusion) younger age (OR, 0.88; 95% CI [0.81–0.95]; $P=0.001$), no previous history of stroke (OR, 0.16; 95% CI [0.039–0.65]; $P=0.010$), and absence of proximal occlusion (OR, 0.183; 95% CI [0.038–0.89]; $P=0.035$) appeared as independent predictors of favorable outcome.

**Moderate Stroke**

A total of 176 patients were included in this group, of which 47.7% were women. The mean age was 72.10±11.38 years. Median NIHSS score on admission was 12 (10–13), and mean time from stroke onset to start of treatment was 172.88±80.28 minutes; 61% of them presented favorable outcome. Proximal occlusion was observed in 64 (38.6%) patients, distal in 79 (47.6%), and in 13 (7.8%) patients the baseline TCD was normal; 52.6%, 68.6%, and 66.7% of patients with proximal, distal, and normal TCD, respectively, achieved a good clinical outcome.

In patients with moderate stroke, there was a significant association between time-to-treatment and functional outcome ($P=0.014$), and a significant trend was between time-to-treatment ≤120 minutes and favorable outcome ($P=0.066$).

Although younger age ($P=0.002$), absence of diabetes mellitus ($P=0.061$), absence of T occlusion ($P=0.013$), absence of initial changes on baseline CT scan ($P=0.016$), and time-to-treatment before 120 minutes ($P=0.066$) were related to favorable outcome in univariate analysis (Table 1), in the multivariate analysis, only age (OR, 0.95; 95% CI [0.92–0.98]; $P=0.003$), no proximal occlusion (OR, 0.362; 95% CI [0.17–0.75]; $P=0.006$), and treatment before 120 minutes (OR, 2.70; 95% CI [1.14–6.38]; $P=0.024$) emerged as independent predictors of favorable outcome.

**Severe Stroke**

A total of 290 patients had severe stroke. Most of them were women (53.1%). The mean age was 74.08±12.15 years, and the median NIHSS score on admission was 20 [18–21]. The mean time-to-treatment was 164.74±74.84 minutes. We observed that 26.2% had favorable outcome. Proximal occlusion was observed in 211 (77.6%) patients, distal in 50 (18.4%), and in 2 (0.7%) patients the baseline TCD was normal; 24.1%, 45.9%, and 0% of patients with proximal, distal, and normal TCD, respectively, achieved a good clinical outcome.

In patients with severe stroke, time-to-treatment was not associated with favorable outcome ($P=0.684$).

As shown in Table 2, younger age ($P<0.001$), better previous mRS ($P=0.006$), female sex ($P=0.108$), and absence of T occlusion ($P=0.031$) were related to favorable outcome. Multivariate analysis including these variables showed that younger age (OR, 0.96; 95% CI [0.94–0.99]; $P=0.001$), lower previous mRS (OR, 0.42; 95% CI [0.21–0.82]; $P=0.011$), and absence of proximal occlusion (OR, 0.48; 95% CI [0.25–0.94]; $P=0.032$) were an independent predictor of favorable outcome in patients with severe stroke.

**Discussion**

The time-dependent effect of thrombolysis with IV tPA on stroke outcome has been consistently demonstrated in meta-analysis of randomized trials. Moreover, several factors have been demonstrated to predict good outcome after IV tPA including milder baseline stroke severity, absence of history of diabetes mellitus, small size and distal location of arterial occlusion, normal CT scan, and normal pretreatment blood pressure.

The present study demonstrates that favorable outcomes vary according to the time from stroke onset to treatment initiation depending on the stroke severity. In patients with mild stroke, time-to-treatment was unrelated to long-term outcome, which may be explained by the high rate of spontaneous recanalization and the inherent favorable outcome in this group of patient, regardless treatment. Conversely, younger age, history of previous stroke, and absence of proximal occlusion emerged as independent predictors of favorable outcome.

Similarly, in patients with severe stroke, there was no association between time-to-treatment and favorable outcome. As expected, this group of patients showed the worse clinical outcome; only 26.2% achieved good favorable outcome. Although the potential lytic resistance of large clot burden may explain in part this observation, we cannot rule out a type II error given the small number of severe strokes achieving good prognosis, which may preclude any association with time-to-treatment. Among patients with severe stroke, younger age was the only independent predictor of favorable outcome.

In contrast, there was a clear time-dependency of IV tPA treatment and long-term outcome in the subgroup of patients with moderate stroke. A cutoff point of 120 minutes emerged as the best predictor for good functional evolution in patients with moderate stroke. This group of patients represents those who, based on baseline characteristics, exhibit a more uncertain prognosis where time-dependency is greater. Moreover, age and absence of proximal occlusion emerged as a strong independent predictor of favorable outcome in all stroke-severity groups. Although no association was found between time-to-treatment and functional outcome in patients with mild or severe stroke, stroke physicians should continue aiming to administer tPA as fast as possible and reduce time-to-treatment.

The impact of time-to-treatment on outcome after thrombolysis mainly depends on factors including the pattern of arterial occlusion, efficacy of collateral circulation, and size of irreversible ischemia. Compared with mild strokes, patients with severe stroke are more likely to have proximal intracranial artery occlusion, lesser degree of collateral flow supply and greater extent of early ischemic changes on CT at the time of tPA administration, leading to a lesser degree of clinical improvement, larger infarct size, and worse long-term outcome. Conversely, mild strokes represent those with distal or even no arterial occlusion, more favorable collateral pattern and good outcome even in cases of no or delayed recanalization. In the subgroup of patients with moderate strokes, good collaterals would ameliorate clinical severity in patients with proximal occlusions and as well as poor collaterals would worsen clinical deficit in patients with distal occlusion. Therefore, noninvasive vascular and tissue evaluation including collateral...
circulation may further refine the predictive accuracy of time-to-treatment on stroke outcome and improve patient stratification in acute reperfusion trials in stroke.

Conclusions

The impact of time-to-treatment on favorable outcome varies widely depending on baseline stroke severity. The window for favorable outcome was ≤120 minutes for moderate strokes. However, time-to-treatment seemed unrelated to functional outcome in mild and severe stroke, probably because of the stronger influence of stroke severity on favorable and unfavorable outcomes, respectively.

Disclosures

Drs Rodriguez-Luna and Flores hold a “Río Hortega” research training contract from the Carlos III Health Institute (Spanish Ministry of Science and Innovation) and the Vall d’Hebron Research Institute. The other authors report no conflicts.

References

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