Impact of Time to Treatment on Tissue-Type Plasminogen Activator–Induced Recanalization in Acute Ischemic Stroke

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Background and Purpose—Although tissue-type plasminogen activator (tPA) efficacy depends on time, it is unknown whether its effect on recanalization is time dependent. Information about likelihood of successful recanalization as a function of time to treatment may improve patient selection for advanced reperfusion strategies. We aimed to identify the impact of time to treatment on tPA-induced recanalization in patients with acute ischemic stroke.

Methods—Consecutive patients with intracranial acute occlusion treated with intravenous tPA underwent transcranial Doppler examination before and 1 hour after tPA administration. Patients were categorized according to occlusion localization in proximal and distal occlusion. Sequential analysis of recanalization according to time to treatment was performed for every 30-minute cutoff point.

Results—Overall (n=508), 54.3% had proximal and 45.7% had distal occlusion. Median time to treatment was 171.4±61.9 minutes, and 5.9% were treated >270 minutes. Recanalization occurred in 36.1% of patients. There was no linear association between time to treatment and time to recanalization, but sequential analysis showed that patients treated >270 minutes had a lower recanalization rate. Lower National Institutes of Health Stroke Scale score on admission (odds ratio [OR], 0.305; 95% confidence interval [CI], 0.1–0.933) and time to treatment ≤270 minutes (OR, 0.995; 95% CI, 0.99–0.999) emerged as independent predictors of recanalization. In patients with proximal occlusion, 41.8% recanalized. Time to treatment >90 minutes was associated with lower recanalization rate. However, only younger age (OR, 0.975; 95% CI, 0.952–0.999) and lower baseline National Institutes of Health Stroke Scale score (OR, 0.921; 95% CI, 0.855–0.993) independently predicted recanalization. In distal occlusion patients, male sex was the only independent predictor of recanalization (OR, 0.416; 95% CI, 0.195–0.887). None recanalized >270 minutes.

Conclusions—The effect of tPA on recanalization may decrease over time. Treatment >270 minutes predicted lack of recanalization, especially in distal occlusions. (Stroke. 2014;45:2734-2738.)

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

See related article, p 2555.

Since 1994, thrombolysis treatment with alteplase (tissue-type plasminogen activator [tPA]) before 3 hours in acute stroke has been the only therapy approved for this disease, and it is associated with improved functional outcome in acute ischemic stroke.1–4 Initially, studies such as National Institute of Neurological Disorder 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.5,7 Afterward, studies such as ECASS III and Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SIST-ISTR) have demonstrated that safety and functional outcomes are less favorable after 3 hours, but the wider time window till 4.5 hours also offers an opportunity for some patients.8,9 Early artery reopening has been recognized as a surrogate marker of good outcome after tPA therapy.10,11 However, recanalization is achieved in only 30% to 40% of patients, and <50% of them become independent at long term.12,13 There is evidence that recanalization after intravenous tPA is influenced by several factors, including size and location of arterial occlusion, atrial fibrillation, and diabetes mellitus.14–16 Although the efficacy on functional outcome of thrombolytic treatment depends on time, it is not clear whether the effect of intravenous tPA on recanalization is also time dependent.

Therefore, we aimed to identify the impact of time to treatment on tPA-related recanalization in patients with acute ischemic stroke.

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Subjects and Methods

Study Population
We prospectively evaluated consecutive patients with acute ischemic stroke treated with intravenous tPA from March 2001 to December 2012. We include 508 consecutive patients with a transcranial Doppler (TCD) occlusion treated according to the criteria of the European Summary of Product Characteristics for tPA treatment until 4.5 hours. Patients with 4.5 to 6 hours from symptoms onset were treated with intravenous tPA and included in the study after selection by emergent MRI, according to a local protocol approved by the local ethics committee. Patients with unknown symptoms onset or wake-up stroke and those with posterior circulation occlusion (basilar artery or vertebral artery occlusion) or those who underwent endovascular treatment were excluded from the analysis.

Clinical Assessment
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. 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 30–60, time-to-treatment >60, and so on.

Stroke severity at baseline was assessed with the National Institutes of Health Stroke Scale (NIHSS) score by a certified neurologist. Early clinical improvement or deterioration were defined by a decrease or increase ≥4 points on the NIHSS score at 24 hours, respectively. Functional outcome was evaluated by the modified Rankin scale at 3 months, and patients were considered independent if their modified Rankin Scale was ≤2.

Transcranial Doppler Ultrasound Protocol
A standard transcranial Doppler (TCD) examination was performed before tPA administration using 1-channel 2-MHz equipment (TCD 100 mdL, Spencer Technologies, and DWL Multidop x4) to assess the presence and location site of vessel occlusion. The examination was repeated 1 hour post-thrombolysis for assessment of vessel recanalization.

Proximal 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 Thrombolysis In Brain Ischemia grading system (grade 0–1).13 Distal MCA occlusion was defined as blunted or dampened signals (Thrombolysis In Brain Ischemia grade 2–3) in the symptomatic artery with <30% flow than the contralateral MCA and flow diversion signs in ipsilateral neighboring arteries.15

Patients were categorized according to the occlusion location into 2 groups: proximal occlusion (n=276) and distal occlusion group (n=232).

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.15 We considered recanalization when complete or partial recanalization was achieved. No change in the abnormal waveforms indicated that no recanalization had occurred.

Neuroimaging Protocol
On admission, patients underwent a computed tomographic scan within the first 4.5 hours after stroke onset. Computed tomographic scans were assessed for the presence of early parenchymal ischemic changes (to rule out lesions more than one third of the MCA territory). In patients with symptoms onset between 4.5 and 6 hours, an emergent multimodal MRI was performed. When the ischemic lesion on diffusion-weighted imaging was less than one third of the MCA territory without lesion on Fluid-Attenuated Inversion Recovery (FLAIR), and a demonstration of an intracranial occlusion on MRI with mismatch >20% between diffusion-weighted imaging and perfusion-weighted imaging was detected, the patient received intravenous tPA.
At 24 hours, a control computed tomography was performed to rule out hemorrhagic transformation.

**Statistical Analysis**

Descriptive and frequency statistical analyses were obtained using IBM SPSS 17.0 software. The categorical variables are presented as absolute values and percentages, and the continuous variables are presented as means±SD if normally distributed or median (interquartile range) 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 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-treatment30, time-to-treatment60, time-to-treatment90, and so on. Figures show a simplified representation of the sequential analysis with the most relevant cutoff points.

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 multivariable model. A P value of ≤0.05 was considered significant for all tests.

**Results**

The main baseline characteristics of the series are summarized in Table 1. Five hundred eight patients were finally included. Mean age of the series was 73.03±12.21 years, and 248 (48.8%) patients were women. Median baseline NIHSS score was 16 (interquartile range, 10–19). Mean time from symptoms to intravenous tPA was 171.4±61.9 minutes, and 28 (5.9%) of all patients were treated after 270 minutes. The time to treatment has been similar along the 7-year period of our study. Recanalization occurred in 155 (36.1%) patients of all treated patients. Early clinical improvement was observed in 258 (51.2%) patients. A good outcome at 3 months was achieved in 197 (45.6%) patients.

On baseline TCD, 276 (54.3%) patients had proximal occlusion, and 232 (45.7%) patients showed distal occlusion. There were no significant differences in baseline clinical characteristics according to time.

We could not find a linear association between time to treatment and recanalization, but the sequential analysis every 30 minutes from onset showed that patients treated after 270 minutes had a lower recanalization rate. Figure 1 shows a simplified representation of the sequential analysis with the most relevant cutoff points.

The variables associated with recanalization in this series were younger age (P=0.046), normal glycemia (P=0.017), and time to treatment before 270 minutes (P=0.032).

After adjusting for representative variables (age, sex, NIHSS score on admission, hyperglycemia, and time to treatment ≥270 minutes) in the regression logistic model, higher NIHSS score on admission (odds ratio [OR], 0.305; 95% confidence interval [CI], 0.1–0.933; P=0.037) and time to treatment ≥270 minutes (OR, 0.995; 95% CI, 0.99–0.999; P=0.030) emerged as independent predictors of lack of recanalization in the global series (Table 2).

**Proximal Occlusion**

From 276 patients with proximal occlusion, 53.3% were women, with a mean age of 72.8±12.65 years. Median NIHSS score on admission was 18 (interquartile range, 15–21) and the mean time from onset to treatment was 170.29±59 minutes. Recanalization was observed in 41.8% of them.

Although time to treatment did not predict recanalization in these patients (P=0.368), the cutoff point time to treatment >90 minutes showed a trend toward lower recanalization in the univariate analysis (P=0.1; Figure 2).

Variables associated with recanalization in proximal occlusion patients are shown in Table 3. After adjusting for

### Table 2. Variables Independently Related to Recanalization by Multiple Logistic Regression Analyses in All, Proximal, and Distal Occlusion Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Proximal Occlusion</th>
<th>Distal Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>P Value</td>
<td>OR  95% CI</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.98 0.966–1.002 0.084</td>
<td></td>
<td>0.975 0.952–0.999 0.039*</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.308 0.839–2.037 0.236</td>
<td></td>
<td>1.020 0.566–1.836 0.945</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.025 0.984–1.069 0.235</td>
<td></td>
<td>0.994 0.988–1.001 0.076</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.305 0.1–0.933 0.037*</td>
<td></td>
<td>0.921 0.855–0.993 0.033*</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

CI indicates confidence interval; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Variables included in the multivariable model (P<0.1).
degree variables, younger age (OR, 0.975; 95% CI, 0.952–0.999; \( P = 0.039 \)) and lower NIHSS score on admission (OR, 0.921; 95% CI, 0.855–0.993; \( P = 0.033 \)) appeared as independent predictors of recanalization.

### Distal Occlusion

Two hundred thirty-two patients were included in this group (Table 3), and 43.5% were women. The mean age was 73.28±11.69 years. Median NIHSS score on admission was 11 (interquartile range, 8–15) and mean time from stroke onset to start of treatment was 172.67±65 minutes. Recanalization was detected in 28.6% of them. No recanalization after 270 minutes was detected in this group of patients.

In patients with distal occlusion, time to treatment was not associated with recanalization (\( P = 0.368 \)), but there was a trend toward lower recanalization in the >270 minutes cutoff point (\( P = 0.081 \); Figure 3).

Only male sex (OR, 0.416; 95% CI, 0.195–0.887; \( P = 0.023 \)) emerged as independent predictor of recanalization in the logistic regression analysis.

### Discussion

Recanalization has consistently demonstrated to be an independent predictor of good functional outcome in the literature.\(^{10,11}\) Several factors have been shown to affect the success of tPA-induced recanalization.\(^{14-16}\) In line with previous reports,\(^{19}\) we observed that hyperglycemia, older age, and female sex predicted lack of recanalization in our patients. Although longer time to treatment has been classically associated with poor functional outcome independent of the vessel status,\(^{20}\) the link between time to treatment and recanalization has not been properly explored in prospective cohorts of patients treated with intravenous tPA.

In the present study, we were unable to demonstrate a linear association between time to treatment and recanalization; however, the sequential analysis each 30 minutes from onset showed that the effect of tPA on recanalization decreases with time. In the global series, the cutoff point >270 minutes emerged as independent predictor of lack of recanalization. Moreover, in distal occlusions, no patient recanalized after 270 minutes. In patients with proximal occlusion, numerically, every 30-minute delay in time to treatment was associated with reduction in recanalization.

Differences between proximal and distal occlusions on tPA-related recanalization have been detected in our study. It is well known that location of intracranial occlusions shows different response to intravenous thrombolysis.\(^{21,22}\) Proximal occlusions represent larger clot burden, which may represent the ideal model to test the decreased efficacy of tPA over time. Even as early as after 90 minutes, there was a trend toward a lower recanalization rate in this group of patients.

The results of this study raise the question of the convenience of extending the time window for intravenous tPA, that is, with multimodal neuroimaging techniques. As the efficacy in terms of recanalization decreases over time, more advanced reperfusion strategies should be explored. After 270 minutes, more intensive lytic therapies could be more efficient (ie, ultrasound-enhanced thrombolysis). Furthermore, in patients with proximal occlusions, the loss of tPA efficacy after 90 minutes favors the idea of the need of more aggressive reperfusion strategies such as endovascular reperfusion therapies.

The potential mechanism of this loss of efficacy of tPA on recanalization is not clear. We hypothesize that there is a
negative selection of patients over time. Late treated patients may have more old, complex, and organized thrombus that have been shown to be more resistant to thrombolysis. Conversely, early treated patients may exhibit fresh, more simple, and less organized clots that have shown to be more prone to be dissolved even by the intrinsic fibrinolysis system.

We also have found an interesting association between NIHSS score at baseline and recanalization, already previously reported.\textsuperscript{23} However, this was not the aim of our study and confounder factors may have influence on this association. Nevertheless, our hypothesis is that in each group, lower baseline NIHSS score could indicate less clot burden and therefore higher probability of recanalization. More studies are necessary to confirm this association.

Our study has some limitations. This is a retrospective study of a prospective database. Although the majority of our patients received intravenous treatment according to the criteria of the European Summary of Product Characteristics for Alteplase, 61 (5.9\%) cases received intravenous tPA after 270 minutes, and this may have influenced the results because of the association of tPA and time to treatment. In this group of patients, we found a lower recanalization rate but this result should be considered cautiously because of the small sample size. Several other factors have been associated with recanalization, such as clot origin, size, location, and composition. We did not focus on these variables specifically in the study, and they may have influence our results. Furthermore, recanalization and reperfusion may have a different impact on clinical outcomes, but we aimed to evaluate the recanalization rate. Different techniques, such as MRI or computed tomography-perfusion would probably differentiate between these 2 phenomena, but were not performed routinely in our patients.

Conclusions

The effect of tPA on recanalization may decrease over time. In our series, treatment after 270 minutes predicted a lack of recanalization, especially in distal occlusions. In proximal occlusions, we observed a trend toward lower recanalization in patients treated after 90 minutes. Our findings suggest that beyond 270 minutes, intravenous fibrinolysis may be insufficient, and therefore, more aggressive therapies could be explored. In proximal occlusions, these intensive therapies may be more effective even after 90 minutes.

Disclosures

Dr Flores holds a Rio 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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