Safety and Efficacy of Intravenous Tissue Plasminogen Activator Stroke Treatment in the 3- to 6-Hour Window Using Multimodal Transcranial Doppler/MRI Selection Protocol

Marc Ribo, MD, PhD; Carlos A. Molina, MD, PhD; Alex Rovira, MD; Manuel Quintana; Pilar Delgado, MD; Joan Montaner, MD, PhD; Elisenda Grive, MD; Juan F. Arenillas, MD, PhD; José Álvarez-Sabín, MD, PhD

Background—Growing data point toward intravenous tissue plasminogen activator (tPA) benefit after 3 hours in selected stroke patients. We aim to study safety and efficacy of tPA treatment in the 3- to 6-hour window using multimodal transcranial Doppler (TCD)/MRI selection criteria.

Methods—We studied patients with acute middle cerebral artery (MCA) occlusion. Patients within 0 to 3 hours from symptom onset (A) were treated according to standard computed tomography criteria. Treatment within 3 to 6 hours (B) was decided according to TCD/MRI protocol. Continuous TCD assessed clot location and recanalization. National Institutes of Health Stroke Scale (NIHSS) at 24 hours assessed neurological improvement/worsening and modified Rankin score <3 functional independence at third month.

Results—Of 135 patients, 56 were in the 3- to 6-hour window. Only 13 (23%) patients within 3 to 6 hours did not meet MRI inclusion criteria. Finally, 122 patients were treated with tPA: A, 79 (65%); B, 43 (35%). Median time to treatment was: A, 136 minutes (range 60 to 180); B, 223 (185 to 360). There were no differences in demographic parameters, baseline NIHSS (A, 17; B, 17; P=0.89), and occlusion location (proximal MCA A, 65.8%; B, 74.4%; P=0.28). Recanalization rates at 2 hours were similar (A, 49.3%; B, 55.2%; P=0.33), as were hemorrhagic transformation rates (asymptomatic: A, 18.7%, B, 26.6%, P=0.43; symptomatic: A, 3.75%, B, 2.38%, P=0.66). Improvement at discharge was similar in both groups (NIHSS dropped 6.3 points [A] versus 6.1 [B]; P=0.86). However, the number of patients who benefited from treatment was slightly higher in the 3- to 6-hour group (A, 58.2%; B, 76.2%; P=0.05), whereas the same rate of patients worsened (A, 11.4%; B, 7.1%; P=0.46). At 3 months, the rate of independent patients was: A, 42% versus B, 38% (P=0.74).

Conclusions—tPA treatment can be safely and effectively extended to the 3- to 6-hour window using TCD/MRI selection criteria. Not using these criteria in the 3- to 6-hour window avoids potentially effective treatment in a high rate of patients. (Stroke. 2005;36:602-606.)

Key Words: computed tomography ■ imaging, diffusion-weighted ■ magnetic resonance angiography ■ stroke, acute ■ thrombolysis ■ tissue plasminogen activator ■ ultrasonography, Doppler ■ ultrasonography, Doppler, transcranial

Tissue plasminogen activator (tPA) is the only approved therapy for acute ischemic stroke; however, it only showed to be effective if administered within 3 hours after symptom onset. Despite the fact that promising data have been reported, no clear benefit of fibrinolytic treatment has been demonstrated for patients treated between 3 and 6 hours after stroke onset, a time period when a substantial number of patients present for evaluation.

tPA helps clinical improvement, achieving early arterial recanalization and reperfusion of the cerebral tissue at risk. The lack of efficacy of tPA may be attributable to an earlier spontaneous reperfusion, the presence of established irreversible brain injury before reperfusion, or the failure to achieve recanalization and reperfusion. In these cases, treatment with tPA is unlikely to produce beneficial effects and may result in harm secondary to brain hemorrhage.
Demographic Data, Risk Factor Profile, and Baseline Clinical Findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=122)</th>
<th>Time to Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–3 hours (n=79)</td>
<td>3–6 hours (n=43)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>Women</td>
<td>47</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>Tobacco</td>
<td>24</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Dystipidemia</td>
<td>36</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>141</td>
<td>141</td>
<td>142</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>156</td>
<td>157</td>
<td>153</td>
</tr>
<tr>
<td>Time to treat (min)</td>
<td>167</td>
<td>136</td>
<td>223</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

| Etiology                  |                      |                   |       |
| Cardioembolic             | 49                   | 52                | 44     | 0.361 |
| Ateroembolic              | 26                   | 25                | 28     | 0.73  |
| Undetermined              | 20                   | 18                | 23     | 0.877 |
| Other                     | 5                    | 5                 | 5      | 0.261 |

Values are mean, median, or percent, as appropriate.

More accessible to the treating physician in the last decade. These diagnostic tools are able to give reliable qualitative information about the perfusion status and the indexes of cellular injury of the newly affected tissue. This information may improve the selection of those patients who are likely to benefit from tPA therapy.12–14 We aim to investigate the potential benefit of tPA therapy beyond the 3-hour window in stroke patients selected with a multimodal TCD/MRI protocol.

**Methods**

From December 2002 to July 2004, all patients with an acute (<6 hours from symptom onset) nonlacunar stroke admitted to the emergency department of a university hospital were prospectively studied. A total of 135 patients with a documented middle cerebral artery (MCA) occlusion were included. Patients were divided in 2 groups according to time from symptom onset: 0 to 3 hours (A) and 3 to 6 hours (B).

### Clinical and TCD Protocol

A detailed history of vascular risk factors was obtained from each patient. To identify potential mechanism of cerebral infarction, a set of diagnostic tests was performed; when indicated, patients also underwent special coagulation tests, transthoracic/transesophageal echocardiography, and Holter monitoring. With the obtained information and the neuroimaging data, previously defined etiologic subgroups were determined (Trial of Org 10172 in Acute Stroke Treatment [TOAST]).15 Clinical examination was performed every hour during the first 6 hours and at 12, 24, and 48 hours after stroke onset. Stroke severity and neurological improvement or worsening were defined as decrease or increase ≥4 points in the National Institutes of Health Stroke Scale (NIHSS).16 A standard TCD examination was performed in the emergency room before tPA administration using 2-MHz equipment. A set of diagnostic criteria was applied to assess arterial occlusion that were defined as previously.6,19 Continuous TCD monitoring during 2 hours after tPA bolus assessed clot location and recanalization rates.17 Favorable outcome at 3 months was defined as modified Rankin score (mRS) ≥0 to 2.

### Imaging Protocol and Treatment Criteria

For all patients in the 3- to 6-hour window, whenever an acute MCA occlusion was detected with TCD, the multiparametric MRI protocol was applied. If patients presented a suboptimal temporal bone window avoiding adequate TCD interpretation, MRI protocol was also applied. Patients in group A were treated according to standard CT-based criteria;7 however, if possible, the MRI protocol was also applied.

The mean MRI examination time (entrance to exit from the MRI suite) was 20 minutes (range 11 to 30 minutes). Details of the multiparametric MRI protocol have been published previously.21 Briefly, MRI was performed with a 1.5T whole body imager system with 24 mT/m gradient strength, 300-millisecond rise time, and an echo-planar–capable receiver equipped with a gradient overdrive (Magnetom Vision Plus; Siemens Medical Systems). The images obtained included the following: axial T2-weighted susceptibility-based echo-planar gradient–echo sequence (0.8/29/1 [repetition time (TR)/echo time (TE)/acquisitions]; total acquisition time 2 seconds); axial diffusion-weighted echo-planar spin–echo sequence (4000/100/2 [TR/TE/acquisitions]; total acquisition time 56 seconds), and axial perfusion-weighted echo-planar gradient echo sequence (2000/60/40 [TR/TE/acquisitions]; total acquisition time 80 seconds).

Diffusion-weighted imaging (DWI) was obtained with a single-shot, spin-echo, echo-planar pulse sequence with diffusion gradient b values of 0, 500, and 1000 sec/mm² along all 3 orthogonal axes over 15 axial sections, with 5-mm-slice thickness (interslice gap of 1.5 mm), a field of view of 230 mm, and 96×128 matrix. The acquisition time for the DWI equaled 56 seconds.
For magnetic resonance angiography, we used a transverse gradient-echo 3D time-of-flight sequence with magnetization transfer suppression and tilted optimized nonsaturating excitation, with 1.5-mm-thick sections (47-mm slab thickness), 200-mm field of view, and 200\times512 matrix. Maximal intensity projection reconstructions were performed at the time of imaging.

Perfusion-weighted imaging (PWI) was acquired by using a bolus of gadolinium-based contrast material (Magnevist; Schering AG) for selected 13- to 15-section positions measured 40\times sequentially. The perfusion-weighted sequence generated a time-to-peak map for each section position that was immediately available for interpretation at the console with all the other images. PWI was obtained using sections 5 mm in thickness, an interslice gap of 1.5 mm, a field of view of 240 mm, and 128\times128 matrix.

For patients in group B, criteria for tPA treatment were defined as a DWI/PWI mismatch >50%; measurement was made by the physicians visually at the console right after image acquisition.

**Follow-Up Imaging and Intracranial Hemorrhage**

In all patients, a CT scan was repeated at 24 to 48 hours to evaluate the presence of intracranial hemorrhage. Whenever a neurological worsening (NIHSS increase >4 points) occurred, an additional CT scan was immediately performed to rule out symptomatic intracranial hemorrhage. All CT scans were reviewed by a neuroradiologist who was blinded to clinical details. Presence and type of hemorrhagic transformation was defined according to previously published criteria.5,7 Hemorrhagic transformations were categorized as symptomatic when a neurological deterioration accompanied the presence of blood at any site in the brain on the CT scan.

**Statistical Analyses**

Descriptive and frequency statistical analyses were obtained and comparisons were made using the SPSS 10.0 statistical package. Statistical significance for intergroup differences was assessed by the Pearson \(\chi^2\) or the Fisher exact test for categorical variables, and the Student \(t\) test and ANOVA for continuous variables. When indicated, nonparametric Mann–Whitney \(U\) and Spearman tests were used. \(P<0.05\) was considered statistically significant.

**Results**

Of the 135 studied patients, 56 were in the 3- to 6-hour window. Only 13 (23%) patients in the 3- to 6-hour window did not meet MRI inclusion criteria. Finally, 122 patients were treated with tPA: A, 79 (65%); B, 43 (35%). Median time to treatment was: A, 136 minutes (range 60 to 180); B, 223 minutes (185 to 360; \(P<0.001\)). There were no differences in demographic parameters, baseline NIHSS (A, 17; B, 17; \(P=0.89\)), occlusion location (proximal MCA: A, 65.8%; B, 74.4%; \(P=0.28\)) or presence of significant ipsilateral internal carotid artery stenosis or occlusion (A, 20%; B, 27%; \(P=0.56\); Table). Recanalization rates at 2 hours were similar (A, 49.3%; B, 55.2%; \(P=0.33\)), as were the hemorrhagic transformation rates (asymptomatic: A, 18.7%; B, 26.6%, \(P=0.43\); symptomatic: A, 3.75%; B, 2.38%, \(P=0.66\); Figure 1). The degree of neurological improvement at discharge was similar in both groups (NIHSS dropped A, 6.3 points; B, 6.1; \(P=0.86\); Figure 2). However, the number of patients who benefit from treatment (NIHSS decreased ≥4 points) was slightly higher in the 3- to 6-hour group (A, 58.2%; B, 76.2%; \(P=0.05\)), whereas the same rate of patients worsened (A, 11.4%; B, 7.1%; \(P=0.46\); Figure 3). In both groups, neurological improvement was related to early recanalization (Figure 4). At 3 months, the rate of functionally independent patients (mRS <3) was: A 42% versus B 38% (\(P=0.74\); Figure 2).

**Discussion**

Our study demonstrated that a multimodal TCD/MRI examination can efficiently identify those stroke patients in the 3- to 6-hour window who would benefit from intravenous tPA therapy. Thrombolytic therapy is approved for stroke treatment in the 0- to 3-hour time window, but there is no randomized clinical trial that proved recombinant tPA to be effective outside the 3-hour time window.

In the following hours after the acute occlusion of the cerebral artery, the tissue at risk in the ischemic penumbra is progressively recruited into the infarct core and irrevers-
ibly loses its function. Many factors such as hyperglycemia,\textsuperscript{9,11} neuroinflammatory markers,\textsuperscript{10} or hyperthermia may accelerate this time-dependent process, leading to wide interindividual differences, especially in the 3- to 6-hour window. Thus, for each individual, the time point at which induced reperfusion may still be beneficial and safe varies.

On the other hand, spontaneous recanalization can occur before the 3 hours,\textsuperscript{6} but this phenomenon is not always accompanied by an immediate correlation with clinical improvement in the so-called stunned brain syndrome.\textsuperscript{22} In these cases, the treating physician is unable to suspect early resolution of the occlusion.

The rationale of tPA use remains in its acceleration of clot lysis in the cerebral arteries leading to earlier reperfusion.\textsuperscript{19} Its lack of efficacy may be attributable to establishment of an already sustained lesion or development of spontaneous recanalization. In both cases, tPA administration will not only increase the risk of hemorrhagic transformation but will also exert its cytotoxic effect on the brain cells.\textsuperscript{23,24}

In the 0- to 3-hour window, the short time from symptom onset allowed selection of patients with CT-based criteria. Within this time, it is very likely that the artery remains occluded with a considerable amount of savable tissue at risk.\textsuperscript{6} Beyond this time point, there is a greater heterogeneity among patients, thus information about indexes of cerebral injury and perfusion status become necessary for an adequate selection. Improved brain imaging methods such as TCD or MRI are becoming available in the emergency routine. Our study showed that they constitute valuable diagnostic tools, allowing safe and effective thrombolytic treatment in as high as 77% of the patients in the 3- to 6-hour window. They are even suitable to detect those patients who are not likely to benefit from thrombolytic therapy, avoiding tPA administration; this may explain that a higher rate of patients in the 3- to 6-hour group experienced a neurological improvement.

This study is not designed to demonstrate that tPA should be administrated in the 3- to 6-hour window to stroke patients but to prove that an accurate selection may safely increase the number of treatable patients that, unfortunately with conventional criteria, is generally not >10% of all stroke cases. The criteria for selection may be discussable and vary, depending on the availability of each center.

Conclusions
tPA treatment can be safely and effectively extended to the 3- to 6-hour window using multimodal TCD/MRI selection criteria. Not using these criteria in the 3- to 6-hour window avoids potentially effective treatment in a high rate of patients. Further studies with improved selection methods need to be addressed to enlarge the therapeutic window of tPA administration.

References


Safety and Efficacy of Intravenous Tissue Plasminogen Activator Stroke Treatment in the 3- to 6-Hour Window Using Multimodal Transcranial Doppler/MRI Selection Protocol
Marc Ribo, Carlos A. Molina, Alex Rovira, Manuel Quintana, Pilar Delgado, Joan Montaner, Elisenda Grivé, Juan F. Arenillas and José Álvarez-Sabín

Stroke. 2005;36:602-606; originally published online February 3, 2005; doi: 10.1161/01.STR.0000155737.43566.ad

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
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/36/3/602

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/