MRI Screening Before Standard Tissue Plasminogen Activator Therapy Is Feasible and Safe

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Background and Purpose—MRI screening for thrombolytic therapy may improve patient selection. Alternatively, it may excessively delay treatment and thereby lead to worse outcomes. We hypothesized that times to treatment and outcomes in a stroke center with immediate MRI access and interpretation would not differ from those of the typical clinical practice.

Methods—We compared the results of 120 consecutive patients treated with intravenous tissue plasminogen activator (tPA) within 3 hours of onset at our center with those of the 2 largest multicenter registries of tPA use. In addition to standard criteria, MRI specific eligibility criteria were applied in 97 patients. MRI was not performed in 23 patients because of contraindications to MRI or late patient arrival (>2.5 hours). Outcomes were the modified Rankin Scale (mRS) obtained at 3 months.

Results—Times to treatment (median door-to-needle time 81.5 minutes; median onset-to-needle time 135 minutes) and outcomes (mRS 0 to 1, 40.8%; mRS 0 to 2, 47.5%) were not inferior to those of the typical clinical practice. Door-to-needle time was shorter in computed tomography (CT) screening (67.5±22.5 minutes; n=23) than in MRI screening (86.8±21.5 minutes; n=97; P<0.001). However, outcomes were not different between MRI screening (mRS 0 to 1, 42.3%; mRS 0 to 2, 49.5%) and CT screening (mRS 0 to 1, 34.8%; mRS 0 to 2, 39.1%). Neither times to treatment nor MRI screening was predictive of outcomes.

Conclusion—These data demonstrate that MRI screening before tPA therapy is feasible and not associated with unacceptable times to treatment or outcomes. (Stroke. 2005;36:1939-1943.)

Key Words: magnetic resonance imaging • stroke, acute • thrombolysis

Standard selection criteria of patients for intravenous thrombolysis with recombinant tissue plasminogen activator (tPA) exclude patients at increased risk for hemorrhagic complications, such as those with acute stroke >3 hours from onset, evidence of acute or chronic intracerebral hemorrhage (ICH), or recent stroke, as well as those in whom the diagnosis of acute stroke is uncertain because of hypoglycemia or seizure at onset. Furthermore, the limited time in evaluating tPA candidates increases the concern for errors in diagnosis that is based only on the immediately available clinical information and a normal computed tomography (CT) scan.

Acute multimodal stroke MRI is sensitive to multiple aspects of cerebrovascular pathology, thus it increases diagnostic confidence by providing greater information about ischemia and hemorrhage than CT. It has been proposed that screening for tPA therapy with stroke MRI may improve patient selection and outcome. An alternative hypothesis is that MRI screening may delay times to treatment relative to usual clinical practice and thereby lead to worse outcomes. To investigate for evidence of adverse effects of MRI screening on times to treatment and outcome, we examined our clinical experience using MRI as a screening examination for tPA therapy. We hypothesized that times to treatment and outcomes in a stroke center with immediate MRI access and interpretation would not be inferior to those of the typical clinical practice.

Methods

Patients

This was a prospective study performed at the National Institutes of Health Stroke Center at Suburban Hospital in Bethesda, Md, from August 1, 1999, to September 30, 2004. In establishing our stroke center, we instituted 24-hour in-house MRI technologists and immediate availability and interpretation of CT and MRI scans when a stroke code was called. At the beginning, our stroke clinical care pathway required CT and MRI as part of the evaluation for all acute stroke patients, including those considered for intravenous tPA therapy. In the final 2 years of the study, CT scan became optional for tPA candidates who had MRI. The acute stroke MRI protocol consisted of diffusion-weighted imaging (DWI), fluid attenuation inversion recovery (FLAIR) image, gradient echo T2*-weighted imaging (GRE), magnetic resonance angiography (MRA), and perfusion-weighted imaging (PWI) sequences, which took ~20 minutes in scanner. The detailed MRI protocol has been described previously. MRI was not performed before tPA therapy if the
patient had a contraindication to MRI, if the patient was not cooperative to undergo MRI, or if there was insufficient time to complete the MRI before 3 hours from onset because of late patient arrival (>2.5 hours from onset).

Eligibility criteria for tPA administration at our institution included the conventional National Institute of Neurological Disorders and Stroke (NINDS) criteria, with the addition of specific MRI criteria. MRI-specific inclusion criterion was stroke MRI evaluation diagnostic for acute ischemic stroke in the setting of diagnostic uncertainty, such as hypoglycemia, seizure at onset, or limited neurological evaluation because of sedating drugs (Figure 1). Patients with perfusion deficits without diffusion abnormalities were included. No upper limit of age or upper or lower limit of National Institutes of Health Stroke Scale (NIHSS) score excluded patients from treatment. MRI-specific exclusion criteria included (1) acute lesion appearing hyperintense on T2-weighted image or FLAIR indicative of onset time >3 hours or nonischemic pathology (Figure 2); (2) presence of acute or subacute lesions on DWI outside of clinically symptomatic regions of undeterminate age; (3) normal DWI, PWI, and MRA of good technical quality in the presence of new disabling deficits (diagnosis of ischemic stroke unlikely); or (4) MRI evidence of acute or chronic cerebral hemorrhage or >2 microbleeds on GRE (Figure 3). The exclusion of multiple microbleeds was considered a relative contraindication and was added during the course of the study after 1 patient in the initial study period with multiple microbleeds experienced a symptomatic ICH.

Data were collected under a natural history study of cerebrovascular disease protocol, which was approved by institutional review boards at the NINDS and Suburban Hospital.

**Definitions of Times and Outcomes**

“Onset time” was defined as the time the patient was last known to be without the index symptoms. “Door time” was the time, as documented in the medical record, when patient was triaged at emergency department, or for patients with in-hospital stroke, when patient’s stroke came to medical attention. “Imaging time” was the time, as documented in the CT or MRI header information, when screening CT or MRI began. “Needle time” was the time, as documented in the medical record, when tPA infusion began. Door-to-imaging time (DTIT) was calculated as imaging time—door time in minutes, imaging-to-needle time (ITNT) as needle time—imaging time in minutes, door-to-needle time (DTNT) as needle time—door time in minutes, and onset-to-needle time (OTNT) as needle time—onset time in minutes.

Clinical outcome was determined by modified Rankin Scale (mRS) at 3 months after stroke or the latest record available. We tabulated the number of patients achieving excellent (mRS 0 to 1) or favorable (mRS 0 to 2) clinical outcome. Symptomatic ICH was defined as ICH on GRE or CT performed within 48 hours after onset with a ≥4-point increase of NIHSS or decrease of level of consciousness.

**Analysis**

We compared times to treatment and clinical outcomes of our study population with those of the 2 largest multicenter registries of tPA use in clinical practice, which are the Standard Treatment with Alteplase to Reverse Stroke (STARS) Study and the Canadian ActiVase for Stroke Effectiveness Study (CASES). Then we compared times to treatment and clinical outcomes between CT screening and MRI screening and also between initial period (from August 1999 to December 2001) and latter period (from January 2002 to September 2004) of this study to see whether time delays for thrombolytic therapy improve over time. We also tried to investigate the association between times to treatment and clinical outcomes from our data. Demographics, risk factors, previous antithrombotic use, baseline NIHSS score, admission glucose, systolic and diastolic blood pressure, stroke subtypes, CT versus MRI screening, and symptomatic ICH after tPA therapy were also considered for analysis. For categorical variables, Pearson’s $\chi^2$ test with exact method was used. For continuous variables, Student’s $t$ test or Mann–Whitney U test for 2-group comparison, and ANOVA or Kruskal–Wallis test for 3-group comparison were used appropri-
A forward stepwise multiple logistic regression analysis was performed to identify the independent predictors of clinical outcomes. SPSS for Windows (version 11.5; SPSS Inc.) was used for the statistical analysis.

Results

All 120 consecutive patients treated with intravenous tPA within 3 hours of symptom onset were included in this study. There were 62 men and 58 women, and mean age was $74.2 \pm 15.3$ years (median 77; range 25 to 100). Initial neurologic deficit measured by baseline NIHSS was mild (NIHSS $\leq 6$) in 43 patients (35.8%), moderate (NIHSS 7 to 15) in 37 (30.8%), and severe (NIHSS $\geq 16$) in 40 (33.3%). Median baseline NIHSS score was 10.5 (range 0 to 33). MRI screening was performed before tPA in 97 patients and CT screening in 23. Of the 97 patients screened with MRI, 58 also had a screening CT before tPA. Stroke subtype was large-artery atherosclerosis in 13 patients (10.8%), cardioembolism in 65 (54.2%), small-vessel occlusion in 11 (9.2%), other etiology in 6, and undetermined etiology in 25 (20.8%). Functional outcome was obtained by actual patient contact at 3 months in 86 (72%) patients (range 82 to 138 days after onset). Outcome was obtained before 3 months in 29 (24%) patients who died before 3-month follow-up. In 5 (4%) patients, outcome was obtained at 1 or 2 months (42 to 66 days after onset).

Comparison With Multicenter tPA Registries

Median and interquartile range of DTNT was 81.5 minutes (66.3 to 97.8 minutes) in a total of 120 patients and 85 minutes (73 to 101.5 minutes) in 97 MRI screenings. OTNT was 135 minutes (114.3 to 162 minutes) in 120 patients and 135 minutes (116.5 to 162 minutes) in 97 MRI-screened patients. DTNT and OTNT of our study population were not longer, and the proportion of patients treated within 90 minutes from onset was not lower compared with those of STARS and CASES (Table 1).

DTNT was within 60 minutes in 11 of 23 (47.8%) patients with CT screening only, in 10 of 39 (25.6%) patients with MRI screen only, and in 2 of 58 (3.4%) patients with MRI and CT screenings.

Table 1. Comparison of Times to Treatment and Outcomes Between Our Study and Benchmark Studies

<table>
<thead>
<tr>
<th></th>
<th>NIH-Suburban</th>
<th>MRI Screening</th>
<th>STARS</th>
<th>CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>120</td>
<td>97</td>
<td>389</td>
<td>1135</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>74</td>
<td>74</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Median baseline NIHSS</td>
<td>10.5</td>
<td>9</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>DTNT, min</td>
<td>81.5 (66.3–97.8)</td>
<td>85 (73–101.5)</td>
<td>96 (75–124)</td>
<td>85 (60–110)</td>
</tr>
<tr>
<td>OTNT, min</td>
<td>135 (114.3–162)</td>
<td>135 (116.5–162)</td>
<td>164 (134–176)</td>
<td>155 (130–175)</td>
</tr>
<tr>
<td>Treated within 90 min of onset</td>
<td>9.2%</td>
<td>7.2%</td>
<td>4%</td>
<td>NA</td>
</tr>
<tr>
<td>mRS 0–1</td>
<td>40.8%</td>
<td>42.3%</td>
<td>35%</td>
<td>32%</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>47.5%</td>
<td>49.5%</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>Symptomatic hemorrhage</td>
<td>4.2%</td>
<td>4.1%</td>
<td>3.3%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

NIH indicates National Institutes of Health.

Values in cells denote median (interquartile range) or column % as appropriate.
The proportions of excellent (mRS 0 to 1) and favorable (mRS 0 to 2) clinical outcomes in a total of 120 patients (40.8% and 47.5%) and 97 MRI screenings (42.3% and 49.5%) were not inferior to those of STARS and CASES, and the rate of symptomatic ICH was comparable (Table 1).

Comparison Between CT and MRI Screenings
Clinical and laboratory variables were comparable between CT screening and MRI screening groups. In the comparison between CT screening only (n=23) and all MRI screening (n=97), ITNT (P=0.003) and DTNT (P<0.001) were significantly shorter in CT screening than in MRI screening, whereas OTDT, DTIT, and OTNT were not different. Clinical outcomes and the rate of symptomatic ICH in MRI screening were not inferior to those of STARS and CASES, and the rate of symptomatic ICH was comparable (Table 1).

In the comparison of the 3 groups (CT screening only, CT and MRI screening, and MRI screening only), the MRI screening only group had longer DTIT and comparable ITNT to the CT screening only group but showed better clinical outcomes than the other 2 groups. CT and MRI screening group had longer ITNT and DTNT compared with the other 2 groups (Table 2).

Comparison Between Initial and Latter Period of Study
During the initial period, 43 patients were treated with intravenous tPA compared with 77 during the latter period. Imaging-to-needle time (50.9±15.1 versus 42.2±20.5 minutes; P=0.009) and door-to-needle time (88.6±22.3 versus 80.1±22.9 minutes; P=0.051) between the initial and the latter period were different. Screening imaging between initial and latter period was also different (CT only 16.3% versus 20.8%; CT and MRI 81.4% versus 29.9%; MRI only 2.3% versus 49.4%; P<0.001). Clinical outcomes and rate of symptomatic ICH were not significantly different between initial versus latter period (mRS 0 to 1, 37.2% versus 42.9%; mRS 0 to 2, 46.5% versus 48.1%; symptomatic ICH, 9.3% versus 2.6%).

Predictors of Clinical Outcomes
Younger age, lower baseline NIHSS score, no previous stroke or transient ischemic attack, no history of diabetes, and previous antithrombotic use were independent predictors of excellent and favorable clinical outcomes by multiple logistic regression analysis (data not shown). However, neither times to treatment nor MRI screening was predictive of clinical outcomes by univariate as well as multivariate analyses.

Discussion
Our findings suggest that MRI screening before intravenous thrombolysis within 3 hours of symptom onset is feasible, practical, and safe. The functional outcomes and the rate of symptomatic ICH in our study were not inferior to those of the NINDS trial1, STARS5 and CASES6. Practice and experience with stroke MRI by a dedicated stroke team can significantly reduce the time and effort for completion of stroke MRI protocol. The goal of DTNT of <60 minutes is an important and valuable ideal, but this goal has remained difficult to achieve in routine clinical practice and was not achieved in the average patient in the NINDS tPA trial.7 In our sample, DTNT of <60 minutes was achieved in 25% of patients who had only an MRI screening. We predict that DTNT of <60 minutes may be routinely achievable with the following measures: more frequent prehospital notification of stroke team by emergency medical services personnel, elimination of the requirement of CT scanning to rule out hemorrhage, and more efficient drug preparation and administration. Our data also showed that ITNT and DTNT were shortened during the study period, probably because of elimination of screening CT scan and better organization of stroke team.

In our study, there was no evidence that MRI screening for tPA therapy led to excessive treatment delays or worse outcomes. It has been shown that the probability of benefit from intravenous tPA relative to placebo diminishes as time elapses during the first 3 hours and up to 6 hours after onset of the stroke in the analysis of NINDS trial7 as well as pooled analysis of 3 large intravenous tPA trials,8 which used CT criteria for patient selection. As time from stroke onset ensues, there is also a decreasing probability of a perfusion defect detected by MRI.9 If these 2 observations are related, then one would predict that selection of tPA patients on the basis of the presence of a perfusion defect may mitigate the decreasing therapeutic opportunity with time from onset. Times to treatment had no relation to clinical outcomes in our

### Table 2. Comparison of Times to Treatment and Outcomes Between CT and MRI Screenings

<table>
<thead>
<tr>
<th></th>
<th>CT Screening Only (n=23)</th>
<th>All (n=97)</th>
<th>CT and MRI (n=58)</th>
<th>MRI Only (n=39)</th>
<th>P*</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITNT, min</td>
<td>34 (22–44)</td>
<td>33 (21–51)</td>
<td>48 (35–60)</td>
<td>64 (52–80)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DTNT, min</td>
<td>48 (35–60)</td>
<td>65 (52–80)</td>
<td>90 (77–104)</td>
<td>85 (73–102)</td>
<td>0.014</td>
<td>0.019</td>
</tr>
<tr>
<td>OTNT, min</td>
<td>127 (97–170)</td>
<td>135 (117–162)</td>
<td>135 (117–160)</td>
<td>140 (114–165)</td>
<td>0.32</td>
<td>0.60</td>
</tr>
<tr>
<td>MRI 0–1</td>
<td>8 (34.8%)</td>
<td>41 (42.3%)</td>
<td>18 (31.0%)</td>
<td>23 (59.0%)</td>
<td>0.64</td>
<td>0.019</td>
</tr>
<tr>
<td>MRI 0–2</td>
<td>9 (39.1%)</td>
<td>48 (49.5%)</td>
<td>22 (37.9%)</td>
<td>26 (66.7%)</td>
<td>0.49</td>
<td>0.014</td>
</tr>
<tr>
<td>Symptomatic hemorrhage</td>
<td>1 (4.3%)</td>
<td>4 (4.1%)</td>
<td>4 (6.9%)</td>
<td>0 (0%)</td>
<td>1.0</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Values in cells denote median (interquartile range) or column % as appropriate.
P* are obtained from comparison of 2 groups (CT screenings and all MRI screenings) and P** from comparison of 3 groups (CT screenings, CT and MRI screenings, and MRI screenings).
study. Furthermore, there is some evidence that highly selected patients with stroke MRI can be safely and effectively treated with thrombolitics beyond 3 hours. In a recent study using a thrombolytic treatment algorithm in which patients were treated according to the NINDS CT protocol within 3 hours and according to stroke MRI selection protocol in the 3- to 6-hour time window, the number of patients who benefited from thrombolysis was higher in the MRI group than in the CT group, whereas the rate of symptomatic ICH was comparable. This is supported by a previous observation that perfusion and parenchymal status assessed with MRI was not different between 0 to 3 and 3 to 6 hours after stroke onset. In a recent trial, intravenous desmoteplase administered 3 to 9 hours after stroke onset in patients selected with perfusion–diffusion mismatch is associated with a higher rate of reperfusion and better clinical outcome compared with placebo. These data suggest that with a stroke MRI selection tool, the time window for treating stroke with thrombolytic therapy can be substantially widened and can possibly yield better results than early treatment based on CT.

Furthermore, stroke MRI provides additional findings not identified on CT such as acute parenchymal injury, perfusion–diffusion mismatch, and the site of vessel occlusion. MRI may also provide information of early blood–brain barrier disruption (Hyperintense Acute Reperfusion Marker [HARM] sign) and microbleeds, which may predict an increased risk of tPA-induced ICH. Thus, MRI can help us to identify patients who will most benefit and who have relative contraindications not evident on routine head CT. On the contrary, MRI screening leads to accurate diagnosis of acute stroke in the setting of diagnostic uncertainty, and thereby may make tPA available to appropriate patients who would be deprived of it by conventional criteria. It has also been proven recently in prospective multicenter studies that stroke MRI is as accurate as CT for the diagnosis of acute ICH. In these regards, MRI can be a sole imaging modality for screening of tPA treatment. The core MRI sequences for screening of tPA candidates include GRE, DWI, MRA, and PWI.

Clinical outcomes in our study population tended to be better than those seen in STARS and CASES, although direct comparison between studies is difficult because of different patient characteristics and follow-up length. The STARS collected 1-month outcome data, whereas in CASES and our study, 3-month outcome data were collected. Mean age is higher but median NIHSS score is lower in our study than in other trials (Table 1).

Our study has limitations. First, MRI-specific criteria for the patient selection in this study have not been validated. For instance, whether the presence of microbleeds increases the risk of ICH after thrombolysis is currently unclear. Second, the proportion of patients in which the MRI changed the decision to treat with tPA is unknown because this was not prospectively recorded in our sample. Third, a randomized comparison between CT screening and MRI screening was not performed. Finally, there is a problem of generalization of our results because the discrepancy in times to treatment between CT and MRI would be greater in centers less specialized for emergency stroke MRI.

In conclusion, this study provides evidence that MRI screening before intravenous tPA therapy within 3 hours of symptom onset does not delay times to treatment or lead to worse outcomes relative to usual clinical practice. A larger series would be necessary to assess whether improved safety and efficacy results from MRI screening for intravenous thrombolysis.

References

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