Thrombolysis in Ischemic Stroke Without Arterial Occlusion at Presentation

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Background and Purpose—None of the randomized trials of intravenous tissue-type plasminogen activator reported vascular imaging acquired before thrombolysis. Efficacy of tissue-type plasminogen activator in stroke without arterial occlusion on vascular imaging remains unknown and speculative.

Methods—We performed a retrospective, multicenter study to collect data of patients who presented to participating centers during a 5-year period with ischemic stroke diagnosed by clinical examination and MRI and with imaging evidence of no vascular occlusion. These patients were divided into 2 groups: those who received thrombolytic therapy and those who did not. Primary outcome measure of the study was excellent clinical outcome defined as modified Rankin Scale of 0 to 1 at 90 days from stroke onset. Secondary outcome measures were good clinical outcome (modified Rankin Scale, 0–2) and perfect outcome (modified Rankin Scale, 0). Safety outcome measures were incidence of symptomatic intracerebral hemorrhage and poor outcome (modified Rankin Scale, 4–6).

Results—A total of 256 patients met study criteria, 103 with thrombolysis and 153 without. Logistic regression analysis showed that patients who received thrombolysis had more frequent excellent outcomes with odds ratio of 3.79 (P<0.01). Symptomatic intracerebral hemorrhage was more frequent in thrombolysis group (4.9 versus 0.7%; P=0.04). Thrombolysis led to more frequent excellent outcome in nonlacunar group with odds ratio 4.90 (P<0.01) and more frequent perfect outcome in lacunar group with odds ratio 8.25 (P<0.01).

Conclusions—This study provides crucial data that patients with ischemic stroke who do not have visible arterial occlusion at presentation may benefit from thrombolysis. (Stroke. 2014;45:2722-2727.)

Key Words: magnetic resonance imaging stroke, lacunar thrombolytic therapy tissue-type plasminogen activator

Several randomized control trials have proven the efficacy of intravenous recombinant tissue-type plasminogen activator (r-tPA) in improving clinical outcomes in patients with acute ischemic stroke if administered within 3 to 4.5 hours of onset of symptoms.1–3 Consequently, administration of r-tPA has become standard of care in all patients with acute ischemic stroke without evidence of bleed on noncontrast computed tomographic (CT) scan in the specified time window. r-tPA works by activating plasminogen to convert to plasmin, which lyses fibrin-rich red clots. This in turn leads to recanalization of an occluded artery and potential restoration of blood flow and, if achieved before tissue infarction, may enhance clinical recovery.4 The use of r-tPA in patients without visible or overt arterial occlusion at presentation, therefore, remains questionable. None of the randomized trials studying the efficacy of r-tPA in ischemic stroke were designed to study the differential effect in subtypes of ischemic stroke defined by modern brain and vascular imaging. Vascular imaging before the administration of r-tPA was not reported. A post hoc analysis performed to study the efficacy of r-tPA in subtypes of stroke by National Institute of Neurological Diseases and Stroke (NINDS) r-tPA study group reported beneficial effect of r-tPA in all the stroke subtypes,5 but a blue ribbon review committee found that the subtype data were invalid.6 Ingall et al7 reanalyzed the NINDS r-tPA trial data to address the growing concern of efficacy of r-tPA. Their findings supported the use of r-tPA to treat patients with acute ischemic stroke according to the protocol used in the trial but they also noted that neither of the 2 parts of the trials were sufficiently powered to detect clinically important subgroup effects.

There are several possibilities when a patient presents with clinical findings that suggest brain ischemia but no arterial occlusion is visible on vascular imaging. First, the patient could have an embolic stroke with spontaneous complete

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recanalization or partial recanalization with embolic occlusion of peripheral branch arteries beyond the capability of visualization by MR angiography or CT angiography. There could be isolated occlusion of these peripheral branch arteries without preceding large-vessel occlusion and spontaneous recanalization, but it is unlikely to produce large clinical deficit. Second, it could be a lacunar stroke caused by small-vessel disease. Third, stroke secondary to vasospasm or fourth, a nonvascular cause, such as systemic hypoperfusion, stroke mimics, or a nonorganic cause. Thrombolysis is definitely not indicated in the latter 2 cases, whereas in the former 2 cases, it remains poorly studied.7

Penetrating artery disease–related lacunar strokes are estimated to account for 20% to 30% of ischemic strokes by various stroke registries,6,9 whereas the percentage of embolic strokes with no vascular occlusion at presentation is estimated to be ≈15%.10 Hence, ≈40% of patients presently receive thrombolytic therapy without proven benefit and with some associated risk.

A retrospective cohort study done by Sylaja et al11 did not find benefit from thrombolysis in patients who did not have arterial occlusion at presentation. However, no follow-up imaging confirming the diagnosis of stroke was reported. Hence, there remains a possibility of inclusion of stroke mimics in the study.

We performed a retrospective, observational study to investigate the use of intravenous thrombolysis in patients with ischemic stroke who do not have visible arterial occlusions on CT angiography or MR angiography examinations.

Materials and Methods

Study Design
A retrospective, observational multicenter, international study was performed. Data of patients presenting to 8 participating centers during the past 5 years with ischemic stroke diagnosed by clinical examination and MRI, National Institute of Health Stroke Scale (NIHSS) >4 and no imaging (CT or MR angiogram) evidence of vascular occlusion obtained before the administration of t-PA were collected.

Demographics, clinical syndrome, risk factors for stroke, NIHSS, and imaging findings of all the patients were documented using a standardized data record form. Eligible patients were divided into 2 groups: those who received thrombolytic therapy and those who did not.

Participating Centers
United States: Beth Israel Deaconess Medical Center, Boston, MA; University of California, Los Angeles, CA; Massachusetts General Hospital, Boston, MA; University of Arkansas, Little Rock, AR; University of Kentucky, Lexington, KY.
Europe: Center Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Pitie-Salpetriere Hospital, APHP, University Pierre et Marie Curie, Paris, France.
India: Kokilaben Dhirubhai Ambani Hospital, Mumbai.

Inclusion Criteria
Patients with following features were included in the study:

- Acute ischemic stroke diagnosed by clinical examination and MRI evidence of lesion corresponding to clinical deficit.
- No evidence of arterial occlusion on CT or MR angiogram at presentation, before the administration of t-PA.
- MR diffusion imaging obtained within 48 hours of onset of stroke.

Exclusion Criteria

- Occlusion or significant stenosis defined as >50% of the artery supplying the ischemic area.
- Preexisting morbidity leading to reduced functionality defined as modified Rankin Scale (mRS) >2.

Imaging
Size and location of the infarct were determined by MR diffusion-weighted images. Patients were further subdivided into 4 groups:

- Patients with cortical infarcts.
- Patients with subcortical, thalamic, pontine infarcts with maximum diameter >20 mm.
- Patients with midbrain, medullary, and cerebellar infarcts.
- Patients with subcortical, thalamic, and pontine infarcts with maximum diameter <20 mm.

The first 3 groups were considered to be caused by a large-vessel embolic occlusion followed by spontaneous recanalization or isolated distal branch occlusion (nonlacunar stroke group), whereas the fourth group was considered to be caused by a lacunar stroke.

Outcome Measures

Primary Outcome Measure
The primary outcome measure was excellent outcome at 3 months after stroke, as defined by a Modified Rankin Scale score 0 to 1. Clinical outcomes in subgroups were compared against each other.

Secondary Outcome Measure
The secondary outcome measures were good outcome defined as mRS 0 to 2 and perfect outcome defined as mRs 0. The safety outcome measures were symptomatic intracerebral hemorrhage leading to worsening of clinical deficit defined as increase in NIHSS by ≥4, and the rate of poor outcome at 3 months defined as mRs 4 to 6.

Statistical Analysis
Demographics were compared between the thrombolyzed and nonthrombolyzed groups using Fisher exact test (categorical variables) or Wilcoxon rank-sum test (continuous variables). We computed odds ratios (ORs) for having an excellent outcome (mRs, 0–1) adjusted for known risk factors by the means of logistic regression analyses. The same analyses were performed for the secondary (perfect mRs, 0 and good mRS, 0–2 outcomes) and safety outcomes (mRs 4–6 and symptomatic hemorrhage).

Risk factors were age, sex, NIHSS at presentation, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and smoking. Of these variables, age, NIHSS at presentation, and prevalence of diabetes mellitus were significantly different between the thrombolysis group and nonthrombolysis group.

Data analysis was conducted using PC-SAS version 9.0.1.1. Statistical significance was determined at the 0.05 level.

Ethical Considerations
The study was approved by the institutional review boards of the individual participating centers. Protocol of the study was published earlier.7

Results
Complete data of 256 patients with ischemic stroke who did not have arterial occlusion at presentation were collected. A
total of 103 of these patients received intravenous thrombolysis, whereas 153 patients did not.

As expected, majority of the patients had strokes with mild to moderate initial severity (median NIHSS, 7; interquartile range, 5–11) and had good clinical outcome at 3 months because 66% of all patients had mRS score 0 to 2.

Demographics and prevalence of risk factors of the patients are presented in Tables 1 and 2.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Thrombolysis Group (IQR)</th>
<th>Nonthrombolysis Group (IQR)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* y, median</td>
<td>68.43 (24–94)</td>
<td>63.21 (18–92)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex (men/women), %</td>
<td>58.3/41.7</td>
<td>58.4/41.2</td>
<td>0.94</td>
</tr>
<tr>
<td>NIHSS at presentation (mean)</td>
<td>9.4</td>
<td>8.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>69.4</td>
<td>62.9</td>
<td>0.43</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36.7</td>
<td>19</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>42.9</td>
<td>35.6</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>18.4</td>
<td>32.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>10.2</td>
<td>14.3</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Subgroup analysis was done for nonlacunar and lacunar strokes. Demographics and prevalence of risk factors in each subgroup is presented in Table 2. Nonlacunar stroke accounted for a total of 154 patients, 49 in thrombolysis group and 105 in the non thrombolysis group, whereas lacunar strokes accounted for a total of 102 patients: 54 in thrombolysis group and 48 in nonthrombolysis group.

In the nonlacunar stroke subgroup, the percentage of patients with excellent outcome (mRS, 0–1) was 51% in the thrombolysis group versus 30% in the nonthrombolysis group (P=0.01). The adjusted OR was 4.90 (95% CI, 2.01–11.93; P=0.01). In this subgroup, the adjusted OR for perfect outcome after thrombolysis was 3.90 (95% CI, 1.18–12.80; P=0.02) and for good outcome 3.87 (95% CI, 1.61–9.30; P=0.002). The rate of symptomatic hemorrhage was 6.1% in the thrombolysis group versus 1% in the nonthrombolysis group (P=0.09). The adjusted OR for poor outcome was not significant, P=0.52 (95% CI, 0.19–1.42; P=0.20).

In the lacunar group, the rate of excellent outcome was similar in both groups (65 versus 63%; P=0.84), and the adjusted OR did not reach statistical significance 2.32 (95% CI, 0.83–6.46; P=0.11). The adjusted OR for good outcome was 2.43 but was not statistically significant (95% CI, 0.73–8.13; P=0.18). However, the rate of perfect outcome was higher in the thrombolysis group (37 versus 15%; P=0.01) and the adjusted OR of 8.25 was highly significant (95% CI, 2.37–28.66; P=0.001). They were 2 symptomatic hemorrhages in the thrombolysis group (3.7%) and none in the nonthrombolysis group. The adjusted OR for poor outcome was not significant, P=0.94 (95% CI, 0.22–5.7).

Increase only in the rate of perfect outcome with thrombolytic therapy can possibly be explained by lower NIHSS and better

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**Table 1. Prevalence of Demographic Variables and Risk Factors**

<table>
<thead>
<tr>
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<th>Thrombolysis Group (IQR)</th>
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<th>P Value</th>
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<td>0.07</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
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<td>14.3</td>
<td>0.48</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; and NIHSS, National Institute of Health Stroke Scale.

*P value from Wilcoxon test was performed.

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functional outcome of patients with lacunar stroke at baseline before treatment.

Discussion

Different subtypes of ischemic strokes have different pathophysiology and natural courses. Consequently, all of them may not respond to the same treatment modality. An important limitation of all the randomized intravenous thrombolytic therapy in ischemic stroke trials has been that none of them were designed to study subtypes of strokes. None of them required vascular imaging to be acquired before administration of r-tPA. Consequently, differential effect in subtypes of stroke remains unstudied and questionable. This study made an attempt to bridge this gap.

This retrospective analysis showed that intravenous thrombolysis significantly benefitted the patients who did not have visible vessel occlusions on CT or MR angiogram before administration of r-tPA.

Possible explanation for this observation could be reperfusion of microcirculation by lysis of microemboli in distal small vessels not seen on CT or MR angiogram in patients who have embolic strokes with spontaneous recanalization. In case of lacunar stroke, occlusion of small perforating arteries is unapparent on CT or MR angiogram. Although lacunar stroke is considered to be secondary to intrinsic wall disease, such as lipohyalinosis, in situ formation of microthrombi can be postulated and has been reported as well. Lysis of these emboli or in situ thrombi and consequent revascularization could be responsible for clinical improvement.

Studies in thrombolysed patients based on the level of vessel occlusion have reported best clinical outcomes in the treatment group where there was no vessel occlusion. However, these studies did not compare treated patients with similar controls who did not receive r-tPA, thus questioning the difference made by thrombolysis in the natural course of the disease. It was supported by a study in nonthrombolysed patients, which found best clinical outcome in patients who did not have visible arterial occlusion.

Similar to our study, Sylaja et al compared 52 patients with no arterial occlusion on CT angiogram done before the administration of r-tPA with a matched group of 67 patients who did not receive thrombolysis. At 3 months, both groups were reported to have similar clinical outcomes. However, this study was limited by its small size and absence of imaging evidence of infarct in many patients. Therefore, inclusion of stroke mimics in the study remains a possibility. In addition, the OR for mRS 0 to 1 had nonsignificant 95% CI: 0.6 to 2.6. The statistics were not adjusted for baseline NIHSS, which was greater in the thrombolysed group (median NIHSS in thrombolysed group 11 versus 7 in controls).

Fiebach et al did a post hoc analysis of 3 randomized trials studying the efficacy of desmoteplase in extended time window of 3 to 9 hours based on MRI, namely Desmoteplase in Acute Ischemic Stroke (DIAS), DIAS-2 and Dose Escalation of Desmoteplase in Acute Ischemic Stroke (DEDAS). In the pooled analysis, they found that desmoteplase improved clinical outcomes in patients who had visible arterial occlusion before treatment but not in the patients who did not have any visible arterial occlusion. However, more patients with arterial occlusion had target mismatch on perfusion imaging, 85% versus 63% and the proportion of patients with vessel occlusion or severe stenosis increased with absolute mismatch volume. Patients were treated between 3 and 9 hours of onset of symptoms as opposed to within 4.5 hours in our study. These could explain the conflicting results.

Similarly, De Silva et al did postanalysis of Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and

Table 3. Logistic Regression Analysis Comparing Thrombolysis Group With Nonthrombolysis Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Lower CL</th>
<th>Upper CL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent outcome</td>
<td>3.79</td>
<td>2.95</td>
<td>7.03</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Good outcome</td>
<td>3.42</td>
<td>1.93</td>
<td>6.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Perfect outcome</td>
<td>5.81</td>
<td>2.63</td>
<td>12.82</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.95</td>
<td>0.99</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>0.82</td>
<td>0.46</td>
<td>1.46</td>
<td>0.50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.51</td>
<td>0.78</td>
<td>2.96</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.48</td>
<td>0.23</td>
<td>0.98</td>
<td>0.04</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.10</td>
<td>0.60</td>
<td>1.99</td>
<td>0.77</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.01</td>
<td>0.59</td>
<td>2.05</td>
<td>0.77</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.28</td>
<td>0.49</td>
<td>3.38</td>
<td>0.62</td>
</tr>
<tr>
<td>NIHSS at presentation</td>
<td>0.84</td>
<td>0.78</td>
<td>0.91</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CL indicates confidence interval limit; and NIHSS, National Institute of Health Stroke Scale.
Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution study (DEFUSE) trials and found similar results to Fiebach et al., but their study also had similar differences from our study.

Our study does have methodological limitations, which include its retrospective design and collection of data from different institutes causing sample heterogeneity. Data from multiple institutes were collected because of the limited number of patients in any individual institute who met the inclusion criteria of having had vascular imaging before administration of r-tPA and underwent MRI within 48 hours of stroke onset. Neither is required to be done according to current treatment guidelines. Second, although risk factors that usually affect the clinical outcome of stroke were collected and adjusted for statistical analysis, other variables may exist and were not addressed. However, all these patients met the standard guidelines for administration of r-tPA. Finally, comparing patients who received r-tPA with those who may not be ideal because of underlying reasons for not giving r-tPA that may affect the outcome. The most common reason for not receiving r-tPA to date was late arrival to the hospital. Patients with any other comorbid condition that could have independently affected the outcome were excluded from the study.

One of the major strengths of this study was objective evidence of stroke in the form of demonstration of infarct on MRI was necessary for inclusion of patient into the study. It allowed us to not only exclude stroke mimics but also reliably subtype stroke based on location and size of the infarct. No previous study assessing the effect of vessel occlusion and stroke type has provided such extensive imaging evidence. Studies reporting differential effects in subtype of strokes used data from clinical examination to classify them. Classification based solely on clinical examination has been proven to be inefficient.

In conclusion, this retrospective study demonstrates the efficacy of intravenous thrombolysis in patients with ischemic stroke who have no radiographically demonstrated arterial occlusion at presentation. Both subgroups, nonlacunar and lacunar strokes, were found to have had better clinical outcome after receiving r-tPA. A prospective study to validate these results is needed and is being planned.

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Disclosures
Dr Michiel has received research grants from Swiss Heart foundation, Cardiomet-ChUV, has speaking engagements with Boehringer-Ingelheim, Bayer, St Jude Medical and Coviden and has received honoraria from Pierre Fabre. Dr Singhal receives research support from National Institutes of Health-National Institute of Neurological Disorders and Stroke (award numbers R21NS077442, R01NS051412, and U10NS0867290). Dr Hastak received honoraria from Boehringer-Ingelheim. The other authors report no conflicts.

Table 4. Fisher Exact Test for Comparison Between Safety Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Safety Outcome</th>
<th>Thrombolysis</th>
<th>Nonthrombolysis</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall sample</td>
<td>sIC bleed absent</td>
<td>98 (95.1%)</td>
<td>152 (99.3%)</td>
<td>250 (97.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>sIC bleed present</td>
<td>5 (4.9%)</td>
<td>1 (0.7%)</td>
<td>6 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Nonlacunar stroke</td>
<td>sIC bleed absent</td>
<td>46 (93.9%)</td>
<td>104 (99.0%)</td>
<td>150 (97.4%)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>sIC bleed present</td>
<td>3 (6.1%)</td>
<td>1 (1.0%)</td>
<td>4 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>sIC bleed absent</td>
<td>52 (96.3%)</td>
<td>48 (100.0%)</td>
<td>100 (98.0%)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>sIC bleed present</td>
<td>2 (3.7%)</td>
<td>0 (0.0%)</td>
<td>2 (2.0%)</td>
<td></td>
</tr>
</tbody>
</table>

sIC indicates symptomatic intracranial.

References
3. IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. The Lancet. 2012;379:2352–2363.
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