Protocol Violations in Community-Based rTPA Stroke Treatment Are Associated With Symptomatic Intracerebral Hemorrhage

Alfredo M. Lopez-Yunez, MD; Askiel Bruno, MD; Linda S. Williams, MD; Engin Yilmaz, MD, PhD; Cristina Zurrú, MD; José Biller, MD

Background—Recombinant tissue plasminogen activator (rTPA) is an established treatment for acute ischemic stroke. The rate and type of protocol violations in rTPA use and their effect on patient outcomes in this setting are not well understood.

Objective—The objective of this study was to examine associations between protocol violations and outcomes in community-based rTPA use.

Methods—We reviewed medical records of stroke patients treated with rTPA in 10 acute-care hospitals in Indianapolis from July 1996 to February 1998 and assessed complications and outcome. Retrospective National Institute of Health Stroke Scale (on admission and discharge), Canadian Neurological Scale, and length of hospital stay were calculated. Appropriate use of rTPA was determined by the National Institute of Neurological Disorders and Stroke (NINDS) protocol.

Results—Fifty patients (mean age, 66 years; 76% white; 56% men) were treated by general neurologists (70%), stroke neurologists (24%), or emergency physicians (6%). Mean times to hospital arrival, brain CT, and start of rTPA infusion were 44, 86, and 141 minutes, respectively. In-hospital mortality rate was 10% (4 intracerebral hemorrhage [ICH], 1 cardiogenic shock). Complications were more frequent among patients with protocol violations (n=8) compared with those without all hemorrhages (75% versus 10%, P<0.001), symptomatic ICH (38% versus 5%, P<0.02), and ICH attributable to rTPA, occurring within 36 hours (38% versus 2.4%, P<0.01), respectively.

Conclusions—NINDS protocol violations are relatively common and are associated with symptomatic cerebral and systemic hemorrhages. When the NINDS protocol is strictly followed, hemorrhage rates in community-based rTPA use are similar to those in the NINDS trial. (Stroke. 2001;32:12-16.)

Key Words: intracerebral hemorrhage ■ plasminogen activator, tissue-type ■ stroke, ischemic

Intravenous recombinant tissue plasminogen activator (rTPA) is currently the only approved therapy for acute ischemic stroke within 3 hours of symptom onset. Its efficacy was demonstrated in the multicenter, randomized trial sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). Post hoc analysis of patients treated within 3 hours of stroke in the ECASS I and ECASS II trials suggests a possible clinical benefit. Despite a proven 11% to 13% absolute benefit over placebo in reducing disability at 3 months and sustained benefit at 1 year, rTPA use in acute ischemic stroke remains a source of debate. There are still concerns and questions among physicians about adherence to protocol and intracerebral hemorrhage (ICH) rate in community-based rTPA administration. Physicians may be unaware of certain exclusion criteria. The purpose of our study was to evaluate outcomes in community-based rTPA use and to assess the relation between protocol violations and outcome.

Subjects and Methods

We retrospectively reviewed paramedic and hospital records on all patients (n=50) who were treated with rTPA for acute ischemic stroke in 10 major hospitals in Indianapolis. Patients treated from July 1996 to February 1998 were identified by linking discharge ICD-9 codes for stroke and pharmacy records of rTPA administration. The pharmacy in each participating hospital keeps a computerized record of rTPA use in each instance. To the best of our knowledge, this sample represents all the patients with acute ischemic stroke treated with rTPA in these hospitals in Indianapolis during the study period. Two of the hospitals did not treat any acute stroke patients with rTPA in the specified period. Neurologists in private practice cared for most patients with acute stroke in these hospitals. We classified stroke neurologists as those who completed a stroke fellowship training program.

Using a standardized data extraction form, we recorded patient demographics, stroke risk factors, time of symptom onset, time of arrival to the emergency department, time to CT, time to rTPA administration, ancillary test results, complications, length of hosp-
Results
Fifty patients received intravenous rTPA for acute ischemic stroke in Indianapolis between July 1996 and February 1998. General neurologists in private practice treated most patients (70%), followed by stroke neurologists (24%) and emergency physicians (6%). Two hospitals had a written rTPA protocol and 7 had rTPA available in the emergency room.

Patient demographics, risk factors, prestroke use of aspirin or warfarin, baseline NIHSS, CNS, stroke subtype, mean times to evaluation and treatment, and outcomes are summarized in Table 1. In-hospital mortality rate was 10%, as the result of ICH (n=4) and cardiogenic shock (n=1). Thirty-nine (78%) records had documentation of discussing the risk-benefit of rTPA administration in acute stroke.

Protocol violations occurred in 8 patients (16%), as detailed in Table 2. All hemorrhages, all ICH (symptomatic plus asymptomatic), symptomatic ICH, and ICH within 36 hours were significantly increased in cases with protocol violations (Table 3). Systolic blood pressure and mean arterial blood pressure levels before infusion, median NIHSS, CNS, stroke subtype, and glucose were not associated with ICH. There were no significant differences in blood pressure and admission blood glucose between protocol violation and non-protocol violation groups.

Importantly, when patients were treated according to the NINDS protocol, hemorrhage rates were nearly identical to those published in the trial (symptomatic ICH attributable to rTPA in 2.5%, all symptomatic ICH in 5%, and all hemorrhagic complications in 10%).

Of the 11 hemorrhages, 4 were systemic and 7 were intracerebral. Two of the ICHs were asymptomatic (found incidentally on MRI follow-up scans) and 5 were symptomatic. Four of the symptomatic ICHs occurred within 36 hours of rTPA infusion. The fifth symptomatic ICH occurred 57 hours after infusion in a patient receiving intravenous heparin. Four of the 5 symptomatic ICHs were fatal. Of the 4 systemic hemorrhages, 1 was a large hematoma in the femoral puncture site, 1 was gingival, 1 was gastrointestinal, and 1 was a ruptured abdominal aneurysm in a patient without any history of peripheral vascular disease, occurring 50 hours after rTPA administration. This last patient required several transfusions but survived without neurological deficits.

Discussion
Several studies have reported the experience with rTPA for acute ischemic stroke after the NINDS stroke trial. Most of
TABLE 2. Protocol Violations and Outcome

<table>
<thead>
<tr>
<th>Type of Protocol Violation</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled hypertension</td>
<td>1</td>
<td>Asymptomatic ICH</td>
</tr>
<tr>
<td>Prolonged PT &gt;15 s</td>
<td>1</td>
<td>Asymptomatic ICH</td>
</tr>
<tr>
<td>Severe head trauma (3 wk before infusion)</td>
<td>1</td>
<td>Fatal symptomatic ICH</td>
</tr>
<tr>
<td>Stroke within past 2 wk</td>
<td>2</td>
<td>Fatal symptomatic ICH (n=1)</td>
</tr>
<tr>
<td>Preinfusion heparin use with prolonged aPTT</td>
<td>1</td>
<td>No complication</td>
</tr>
<tr>
<td>Immediate heparin use after rTPA</td>
<td>2</td>
<td>Fatal symptomatic ICH (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No complication (n=1)</td>
</tr>
</tbody>
</table>

Chiu et al\(^\text{15}\) prospectively studied 30 patients in the Houston area treated with intravenous rTPA by an experienced stroke team. Rates of symptomatic ICH, fatal and favorable outcomes, were comparable with the NINDS trial. They concluded that rTPA administration is feasible, safe, and efficacious when guidelines are carefully followed in a non-stroke specialist setting but also highlights the importance of strict adherence to the original protocol.

Grond et al\(^\text{18}\) reported 100 patients with acute ischemic stroke treated with intravenous rTPA by an experienced stroke team. Rates of symptomatic ICH, fatal and favorable outcomes, were comparable with the NINDS trial. They concluded that rTPA administration is feasible, safe, and efficacious when guidelines are carefully followed in an urban setting. Similar results were reported from the Oregon Stroke Center.\(^\text{17}\) Patients were treated following the NINDS protocol and 2 additional criteria: NIHSS of $\geq 4$ and absence of hypodensity in greater than one third of the middle cerebral artery territory on initial cerebral CT. Among 33 patients with mean NIHSS of 14.7, a favorable outcome at 3 months was achieved by 39% (Rankin 0 or 1). Rates of symptomatic and fatal ICHs were 9% and 6%, respectively. No protocol violations were reported.

Grond et al\(^\text{18}\) reported 100 patients with acute ischemic stroke treated with intravenous rTPA, followed by immediate use of intravenous heparin and mannitol or glycerol. Hemorrhagic infarctions and parenchymal hemorrhages occurred in 18%, a third of which were associated with neurological deterioration (6%). Outcomes were slightly better than in the NINDS trial, perhaps because of a younger patient population and lower mean NIHSS. Two deviations from their protocol occurred, both as the results of inaccuracies in the timing of symptom onset, and both were fatal as the result of cerebral edema. Interestingly, immediate use of heparin, a NINDS protocol violation, did not result in higher rates of symptomatic ICH.

Tanne et al\(^\text{16}\) described protocol violations in 30% (56 of 159) of patients and found a trend but no significant association with ICH. Their ICH rate after excluding these violations was also 4%. Buchan et al\(^\text{19}\) reported 68 patients treated with rTPA within 3 hours of stroke onset in a single hospital in Calgary, Canada. Protocol violations were found in 16% of patients who had a lower probability of independence and neurological recovery, as well as a high probability of symptomatic hemorrhage compared with patients treated according to the NINDS protocol. Six of the 11 violations were CT violations and 5 were clinical including prolonged window, thrombocytopenia, dementia, and loss of consciousness. The Standard Treatment with Alteplase to Reverse Stroke (STARS)\(^\text{20}\) investigators found protocol violations in 32.6% of 389 patients treated with rTPA for ischemic stroke in academic and community hospitals. Almost half of the violations were either rTPA administration $>3$ hours after onset of symptoms or use of anticoagulants within 24 hours of treatment. Symptomatic ICH occurred in 3.2% of the patients but no significant difference was found between patients with and those without protocol violations.\(^\text{18}\) This lack of association between symptomatic ICH and protocol deviations has also been reported by Katzan et al.\(^\text{21}\) They described 70 patients treated with rTPA in 29 hospitals in the Cleveland metropolitan area. Symptomatic ICH was found in 15.7% of patients, the highest rate reported to date in the United States. The authors found a trend toward symptomatic ICH in those patients, with no documentation of stroke severity (60% in their cohort) and in those whose blood pressure monitoring deviated from the protocol. Differential effects on ICH risk according to the type of protocol violation may explain the discrepancies between these reports and our results (Table 4). Protocol violations in our community were somewhat different than in the STARS or Cleveland area studies. None of ours were time violations, whereas a large number of violations in STARS (41%) and Cleveland (26%) were of this type. If time violations are not as dangerous as anticoagulation or elevated blood pressure during the 24 hours after infusion, then this may explain in part the lack of association between violations and ICH in these studies. In addition, the reports from Buchan et al (Calgary), Tanne et al (multicenter), and our data have a disproportionate large percentage of “other” protocol violations including head trauma, recent stroke, and abnormalities on CT, among others. These studies found a strong association or a trend for association between violations and ICH, which supports the notion that ICH risk depends on the type of protocol violation rather than on the presence of any violation. Further studies are needed to establish the type of violations with greatest ICH risk.

Our study focused on adherence to published guidelines for intravenous rTPA treatment of acute ischemic stroke in a community-based setting. Previously, we found that only a minority of neurologists and emergency physicians have used rTPA to treat acute ischemic stroke.\(^\text{8}\) When asked about potential contraindications to its use, most of the survey

TABLE 3. Protocol Violations and Hemorrhagic Complications

<table>
<thead>
<tr>
<th>Protocol Violation</th>
<th>No Protocol Violation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hemorrhages</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>All ICH</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ICH within 36 h of rTPA</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
respondents recognized the 3-hour time window but failed to recognize uncontrolled hypertension as a protocol violation. General neurologists or emergency physicians, not stroke specialists, treated 76% of patients in our study. Therefore, our results may be more generalizable to usual clinical settings. Patients’ age, sex, risk factors, and in-hospital mortality rates were comparable to the NINDS trial. The median admission NIHSS in our study is lower than in the NINDS trial (11 versus 14), but symptomatic and fatal ICH rates are higher in our study, probably because of the deviations from the protocol. When the NINDS protocol was followed, symptomatic and fatal ICH rates in our study were similar to those in the NINDS trial.

Our results support the need for strict adherence to the NINDS rtPA protocol for treatment of acute ischemic stroke. In our study, recent stroke (within the past 2 weeks of index stroke) and immediate heparin use after rtPA infusion accounted for half of the violations and 2 of the symptomatic ICHs. In the absence of a written protocol, physicians may remember the time window but may not remember the important, less obvious contraindications. Educational efforts should stress these clinical contraindications as well as the avoidance of antiplatelet or anticoagulant agents for 24 hours after infusion of rtPA in acute stroke, a relevant difference from the rtPA protocol for myocardial infarction.

In addition to improving adherence to the thrombolysis protocol, some other aspects of rtPA delivery may also be improved. Infusion of rtPA was started \( \approx 100 \) minutes after arrival to the emergency room and \( \approx 70 \) minutes after CT. Both time periods are beyond the recommended Advanced Cardiac Life Support (ACLS) guidelines.\(^2\) These times may be shortened by prompt neurologic consultation or stroke team activation (where available), by implementation of a thrombolysis protocol, and by ensuring rtPA availability in emergency rooms.

This study has some limitations. It is relatively small and retrospective, and data extractors were not systematically blinded to patients’ outcome. However, we attempted to enhance the uniformity of data collected by using a standardized data collection sheet for documentation of adherence to protocol.

Our results show that protocol violations in community-based rtPA administration for acute stroke are associated with serious complications. Conversely, when the protocol is followed, rtPA may be administered as safely as in the NINDS trial. Periodic physician education efforts about appropriate rtPA administration for acute ischemic stroke may help avoid protocol violations.

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**References**


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**TABLE 4. Type of Protocol Violation and Symptomatic ICH Across Studies**

<table>
<thead>
<tr>
<th>Study* (No. of Protocol Violations)</th>
<th>Treated &gt;3 h After Onset, %</th>
<th>Antiplatlet or Anticoagulant &lt;24 h After TPA, %</th>
<th>Blood Pressure &gt;185/110, mm Hg, %</th>
<th>Elevated aPTT/PT/INR, %</th>
<th>Other, % ‡</th>
<th>Symptomatic ICH, %</th>
<th>Association With Symptomatic ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARS†‡ (n = 127)</td>
<td>41</td>
<td>33</td>
<td>25</td>
<td>18</td>
<td>2.5</td>
<td>3</td>
<td>No (P = 0.7)</td>
</tr>
<tr>
<td>Cleveland‡ (n = 35)</td>
<td>26</td>
<td>74</td>
<td>14</td>
<td>...</td>
<td>...</td>
<td>16</td>
<td>No (P = 0.34)</td>
</tr>
<tr>
<td>Houston‡ (n = 3)</td>
<td>100</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>7</td>
<td>Not reported</td>
</tr>
<tr>
<td>Calgary‡ (n = 11)</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>81</td>
<td>9</td>
<td>Yes (P = 0.05)</td>
</tr>
<tr>
<td>USA multicenter‡ (n = 56)</td>
<td>8</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>70</td>
<td>6</td>
<td>No (P &lt; 0.09)</td>
</tr>
<tr>
<td>Indianapolis (n = 8)</td>
<td>0</td>
<td>25</td>
<td>13</td>
<td>25</td>
<td>38</td>
<td>10</td>
<td>Yes (P &lt; 0.02)</td>
</tr>
</tbody>
</table>

*Studies that followed NINDS protocol and reported violations are included. †Patients may have >1 protocol violation. ‡See text for exclusions (Reference 12).


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