An Expedited Code Stroke Protocol Is Feasible and Safe

Justin A. Sattin, MD; Scott E. Olson, MD; Lin Liu, PhD; Rema Raman, PhD; Patrick D. Lyden, MD

Background and Purpose—Stroke recovery critically depends on timely reperfusion. In July 2003, we set a benchmark onset-to-treatment time of ≤2 hours and instituted an expedited code stroke protocol to accomplish this. We aim to show that the protocol is feasible and safe.

Methods—The expedited protocol includes: Benchmark onset-to-treatment within 2 hours; in-person triage of all code stroke patients; unmixed tissue plasminogen activator at the bedside during evaluation; no delays pending coagulation tests, chest x-ray, or stool guiac unless specifically indicated; and no delays pending formal CT interpretation or written consent.

Results—Between July 2003 and June 2005, we evaluated 781 patients and treated 103 of 781 (13.2%) with intravenous recombinant tissue plasminogen activator within 3 hours. Of these, we treated 49 of 103 (47.6%) within 2 hours of symptom onset, and 54 of 103 (52.4%) between 2 and 3 hours. The overall risk of symptomatic intracerebral hemorrhage was 4 of 103 (3.9%; 95% CI, 1.1%, 9.6%), and not significantly different from 6.4% (P=0.42). The hemorrhage risks in those treated within 2 hours of symptom onset and those treated between 2 and 3 hours were not significantly different from each other or from 6.4%.

Conclusions—The expedited code stroke protocol is feasible and appears safe. Further study is warranted to confirm its safety and determine whether it results in better clinical outcomes. (Stroke. 2006;37:2935-2939.)

Key Words: acute care ■ health resources/utilization ■ stroke management ■ thrombolysis

When given to stroke patients within 3 hours of symptom onset, recombinant tissue plasminogen activator (rt-PA) improves neurological outcome,1 whereas trials including subjects presenting beyond 3 hours failed to demonstrate benefit.2–5 However, pooled analyses suggest that the 3-hour mark does not rigidly demarcate those patients who can expect to benefit from those who cannot. The odds of favorable outcome appear to decline over time,6,7 implying that treatment should be rendered as early as possible and not simply within the 3-hour window.

Before receiving rt-PA, stroke patients must satisfy multiple criteria that require clinical and diagnostic testing.8,9 Lack of adherence to this protocol has been associated with symptomatic intracerebral hemorrhage (sICH) risks exceeding those in the pivotal trials.10,11 However, we observed in San Diego that certain clinical habits not included in the pivotal rt-PA study protocol had crept into the acute stroke evaluation. Examples included delay of treatment pending the results of coagulation studies, chest x-ray, and stool guiac. Absent a priori reason to expect certain abnormal test results (such as when the patient may be taking warfarin), withholding treatment pending those results may cause unnecessary delay. An individualized evaluation may allow patients to be treated faster, without sacrificing safety.

In July 2003, we established a benchmark onset-to-treatment time of 2 hours and implemented an expedited code stroke protocol to accomplish this. The protocol expressly avoids some elements of the evaluation that have become clinical habit, but that we believe contribute little to the determination of the patient’s suitability for thrombolysis. Our aim in this report is to demonstrate the safety and feasibility of the protocol.}

Methods

Code Stroke Protocol

The key features of the expedited code stroke protocol are summarized in Table 1. The protocol is applied to all patients evaluated by the University of California, San Diego stroke team; the only selection that takes place is by the emergency department physicians at our 6 affiliated hospitals, who decide whether to activate the code stroke pager. When the pager is activated, the physician on call immediately proceeds to the bedside. The case is not triaged over the telephone, although preliminary history is obtained by the physician on call while traveling to the site. The practice of avoiding telephone triage eliminates the possibility of excluding patients for whom rt-PA initially seems contraindicated, but who actually qualify for treatment after a more detailed evaluation by the vascular specialist.12

If the initial impression suggests that the patient may benefit from rt-PA, the drug is brought to the bedside unmixed pending further evaluation. When the final treatment decision is made, the drug is immediately mixed and administered, occasionally by the on-call...
physician if the nursing staff is otherwise occupied. If the patient is excluded, the unopened drug box is returned to the pharmacy.

The most important laboratory result we require before treatment is a serum glucose, which can be obtained using a bedside fingerstick test. If the paramedics obtained one in the field, that value is used pending return of the chemistry panel. The pivotal rt-PA study protocol also required a platelet count \( >100,000/\mu\text{L} \). We do not delay treatment pending the results of prothrombin time or partial thromboplastin time unless there is clinical reason to expect an abnormality of these studies. \(^{13}\) Similarly, we do not require a pretreatment stool guaiac or chest x-ray unless there is a specific indication. \(^{14}\)

The CT scan is examined by the on-call stroke physician in the CT control room or on the Picture Archiving Communication System monitor. We do not delay therapy pending the radiologist’s interpretation, but if it becomes available before thrombolytic decision-making, the opinion is used in making the final treatment decision. We also do not delay for written informed consent, but if the patient is able to consent, or family members are nearby, then verbal consent is obtained.

Other aspects of the standard protocol are followed, \(^{14}\) especially exclusions based on time from onset, blood pressure, history of recent myocardial infarction, presentation consistent with subarachnoid hemorrhage, and history of intracranial hemorrhage.

Outcome Definition
In this safety report, the primary outcome is symptomatic intracerebral hemorrhage. This was defined as in the pivotal rt-PA study: worsening of neurological status within 36 hours after rt-PA infusion, associated with an increase of \( \geq 4 \) points on the National Institutes of Health Stroke Scale (NIHSS) and blood on head CT. \(^{1}\)

Data Collection
The data herein represent patients seen between July 1, 2003 and June 30, 2005. The times from symptom onset to rt-PA bolus were recorded prospectively, whereas most safety data were obtained through chart review. Discharge summaries and reports of all follow-up neuroimaging studies were examined for each patient. Any evidence of intracranial bleeding prompted careful review of the daily progress notes for evidence of neurological worsening.

Along with the expedited protocol, we also implemented a database to capture demographic, process of care, safety, and 90-day outcome information. A limited dataset was collected from all

### Table 1. Key Features of the Expedited Code Stroke Protocol

<table>
<thead>
<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>2-hour onset-to-treatment benchmark</td>
</tr>
<tr>
<td>In-person triage of all code stroke calls</td>
</tr>
<tr>
<td>Unmixed rt-PA at the bedside</td>
</tr>
<tr>
<td>Proceed without coagulation test results unless specifically indicated</td>
</tr>
<tr>
<td>Proceed without chest x-ray unless specifically indicated</td>
</tr>
<tr>
<td>No delay for formal CT interpretation</td>
</tr>
<tr>
<td>No delay for written consent</td>
</tr>
</tbody>
</table>

### Table 2. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=282)</th>
<th>All Treated (n=45)</th>
<th>Treated ( \leq 2^\text{h} ) (n=20)</th>
<th>Treated ( 2^\text{h} ) to ( 3^\text{h} ) (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean±SD</td>
<td>67±16</td>
<td>68±16</td>
<td>64±16</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>70 (22–96)</td>
<td>74 (36–93)</td>
<td>68 (36–87)</td>
</tr>
<tr>
<td>Female, %</td>
<td>48</td>
<td>43</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>White, %</td>
<td>77</td>
<td>77</td>
<td>70</td>
<td>83</td>
</tr>
<tr>
<td>Black, %</td>
<td>13</td>
<td>18</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>NIHSS</td>
<td>Mean±SD</td>
<td>9.5±8.4</td>
<td>14.1±7.0</td>
<td>15.2±6.0</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>7 (0–38)</td>
<td>14 (3–30)</td>
<td>14.5 (3–28)</td>
</tr>
<tr>
<td>Edema on CT, %</td>
<td>19</td>
<td>28</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>Hx of HTN, %</td>
<td>66</td>
<td>71</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Hx of diabetes, %</td>
<td>21</td>
<td>23</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>Mean±SD</td>
<td>7.7±3.4</td>
<td>7.8±3.3</td>
<td>7.2±2.3</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>6.5 (3.1–27.4)</td>
<td>6.7 (4.7–18.0)</td>
<td>6.4 (5.0, 14.6)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>Mean±SD</td>
<td>139±61</td>
<td>140±59</td>
<td>130±42</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>117 (56–494)</td>
<td>120 (85–324)</td>
<td>115 (90–262)</td>
</tr>
</tbody>
</table>

### Figure 1. Distribution of stroke severity. The 2- to 3-hour cohort had more patients with mild deficits.
registered patients with Institutional Review Board (IRB)-approved waiver of consent; those who received rt-PA were asked to provide consent to be contacted 90 days later to determine their functional outcomes.

**Statistical Analysis**

Descriptive statistics were used to summarize the demographic and other baseline characteristics, process times, and sICH rates. The differences in the demographic and baseline characteristics between patients treated within 2 hours and those treated between 2 and 3 hours were assessed using Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. An exact binomial test was used to determine whether the sICH rate among all treated patients was significantly different from 6.4%, and 95% confidence intervals for the sICH rates were calculated. Fisher’s exact test was used to compare the sICH rates between patients treated within 2 hours and those treated between 2 and 3 hours.

**Results**

**Treatment Rate**

Between July 2003 and June 2005, we evaluated 781 patients and treated 103 of 781 (13.2%) with intravenous rt-PA within 3 hours of symptom onset. Of these, 49 of 103 (47.6%) were treated within 2 hours of onset, and 54 of 103 (52.4%) were treated between 2 and 3 hours.

**Hemorrhage Risk**

Follow-up through 36 hours after infusion was completed for 102 of 103 (99.0%) of rt-PA–treated patients. The remaining patient was a homeless man whose left hemiplegia completely resolved during rt-PA infusion and who then left the emergency department against medical advice. Beginning 4 months later, he re-presented several times with the symptom of left-sided weakness. Multiple noncontrast head CTs showed right parietal encephalomalacia consistent with remote ischemic infarction; there was no evidence of previous hemorrhage, and thus he is not counted among the symptomatic intracerebral hemorrhages.

The overall risk of symptomatic intracerebral hemorrhage was 4 of 103 (3.9%; 95% CI, 1.1%, 9.6%), and not significantly different from 6.4% ($P=0.42$). In the $\leq2$-hour group, the risk was 2 of 49 (4.1%; 95% CI, 0.5%, 14.0%). In the 2-
to 3-hour group, the risk was 2 of 54 (3.7%; 95% CI, 0.5%, 12.7%). These risks were not significantly different from each other ($P=1.0$).

**Demographics and Process of Care**

Table 2 shows the demographic and baseline characteristics of the patients for whom a code stroke was activated. Although there were no statistically significant differences between the ≤2-hour and the 2- to 3-hour patients, Figure 1 shows that the 2- to 3-hour cohort had more patients with NIHSS scores 0 to 5.

The median time from symptom onset to hospital arrival was 15 minutes longer in the 2- to 3-hour patients compared with the ≤2-hour patients, but the median time from symptom onset to rt-PA bolus was 44 minutes longer (Table 3 and Figure 2). This implies that the delay to arrival did not completely explain the delay to treatment. Table 3 and Figure 3 show that after hospital arrival, most steps in the process of care occurred at about the same time in the 2 groups except for the treatment decision, which took an additional 21 minutes in the 2- to 3-hour group.

**Discussion**

In the interest of earlier treatment, the expedited code stroke protocol avoids delays for tests that we believe contribute little to the evaluation of the patient’s suitability for thrombolysis. The protocol appears safe, although our present sample size yields limited power to detect a sICH risk significantly different from 6.4%. We can assert only that it causes no obvious and significant harm. More experience will be necessary to confirm whether occasional mistakes, made in haste, lead to measurable increases in adverse events. Because previous authors have shown significant benefit from earlier treatment,6,7 we also expect to find improved 90-day outcomes in the 2-hour group compared with the 2- to 3-hour group. Our ongoing registry will continue to amass patient experience to address this question while maintaining considerable attention to safety.

Almost half of those who received rt-PA were treated within 2 hours of symptom onset. Notably, the delay to hospital arrival did not fully explain the delayed treatment times in the 2- to 3-hour group. The extra 21 minutes from door to decision in the 2- to 3-hour group suggests the
possibility that once the 2-hour benchmark is past, the team relaxes and makes use of the additional time before the next benchmark, 3 hours. An alternative explanation is that because the 2- to 3-hour cohort had more patients with mild deficits, the team paused for further observation of, or more detailed discussion of risks and benefits with, these patients before deciding to proceed with thrombolytic therapy. Finally, it is possible that factors intrinsic to the individual hospitals played a role. Our sample is too small to permit meaningful stratification by site, and further study is needed to explain this excess treatment delay.

Lacking a control group or comparable data before 2003, we cannot prove that the expedited protocol caused more treatments within 2 hours compared with our previous practice. However, our 47.6% of treated patients who received rt-PA within 2 hours of symptom onset does compare favorably with reports from investigators in Houston (28%) and Canada (20.8%).

The expedited code stroke protocol may be appropriate in settings in which therapy other than intravenous rt-PA is planned. We designed the protocol to expedite the time to decision, which could just as easily be the decision to take the patient for an interventional procedure or to use neuroprotectants. Caching the unmixed thrombolytic at the bedside, however, is a key provision of this expedited protocol; in an interventional setting, this idea would require a similar pre-positioning of resources, likely in the form of an in-house or rapid-response angiography team. Prepositioning a neuroprotectant would be simple, perhaps even allowing in-field treatment in some circumstances.

Our results must be viewed in light of some limitations. Throughout the 2-year period, we collected complete data on the number of code stroke patients seen and treated, and the times from symptom onset to rt-PA bolus. However, most of the 36-hour safety outcomes were determined retrospectively. Our careful chart reviews should minimize, but cannot eliminate, the possibility of missing a symptomatic hemorrhage. Detailed demographic, baseline, and process of care data are only available for a subset of our patients because of the learning curve associated with implementation of a new database. This subset may not be representative of the entire cohort. Another limitation is the relatively small sample size, which limits our conclusions to feasibility and a tentative conclusion of safety at the grossest level.

Conclusions

Our expedited code stroke protocol is feasible and appears safe. Further study is warranted to confirm its safety and determine whether it results in better clinical outcomes.

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Disclosures

None.

References

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