Intravenous Tissue-Type Plasminogen Activator Therapy for Ischemic Stroke

Houston Experience 1996 to 2000

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Context: Intravenous tissue-type plasminogen activator (tPA) therapy using the National Institute of Neurological Disorders and Stroke criteria has been given with variable safety to less than 5% of the patients who have ischemic strokes nationwide. Our center is experienced in treating large numbers of stroke patients with intravenous tPA.

Objective: To report our total 4-year experience in the treatment of consecutive patients who had an ischemic stroke.

Design: Prospective inception cohort registry of all patients seen by our stroke team and an additional retrospective medical record review of all patients treated between January 1, 1996, and June 1, 2000.

Setting: A veteran stroke team composed of fellows and stroke-specialty faculty servicing 1 university and 3 community hospitals in a large urban setting.

Patients: Consecutive patients with ischemic stroke treated within the first 3 hours of symptom onset.

Intervention: According to the National Institute of Neurological Disorders and Stroke protocol, 0.9 mg/kg of intravenous tissue-type plasminogen activator was administered.

Main Outcome Measures: Number and proportion treated, patient demographics, time to treatment, hemorrhage rates, and clinical outcome.

Results: A total of 269 patients were treated between January 1, 1996, and June 1, 2000. Their mean age was 68 years (age range, 24-93 years); 48% were women. This represented 9% of all patients admitted with symptoms of cerebral ischemia at our most active hospital (over the final 6 months, 13% of all patients with symptoms of cerebral ischemia and 15% of all acute ischemic stroke patients).

Before treatment the mean±SD National Institutes of Health Stroke Scale (NIHSS) score was 14.4±6.1 points (median, 14 points; range, 4-33 points). A tPA bolus was given at 137 minutes (range, 30-180 minutes); 28% of the patients were treated within 2 hours. The mean door-to-needle time was 70 minutes (range, 10-129 minutes). The symptomatic intracerebral hemorrhage rate was 5.6% of those patients with a second set of brain scans (4.5% of all patients), with a declining trend from 1996 to 2000. Protocol violations were found in 13% of all patients; the symptomatic intracerebral hemorrhage rate in these patients was 15%.

At 24 hours, the NIHSS score was 10±8 points (median, 8 points; range, 0-36 points). In-hospital mortality was 15% and the patients’ discharge NIHSS scores were 7±7 points (median, 3 points; range, 0-35 points).

Conclusions: Intravenous tPA therapy can be given to up to 15% of the patients with acute ischemic stroke with a low risk of symptomatic intracerebral hemorrhage. Successful experience with intravenous tPA therapy depends on the experience and organization of the treating team and adherence to published guidelines.
SUBJECTS AND METHODS

Between January 1, 1996, and June 1, 2000, all patients treated by our stroke team with IV tPA within 3 hours from stroke onset following established guidelines at our university teaching hospital and 3 community hospitals were prospectively identified. Our stroke team participated in the NINDS rt-PA Stroke Study Group, has been in place since 1986, and has been described in previous publications. In brief, a dedicated stroke beeper is carried by all fellows and faculty who constitute our stroke team. The beeper number is only available to the City of Houston Fire Department Emergency Medical Services (HFD-EMS) paramedics and the emergency department (ED) triage nurses of our 4 participating hospitals. Paramedics and ED nurses are regularly in-service to emphasize early and accurate recognition of patients with acute stroke and to institute an acute stroke management pathway that includes immediate notification of our stroke team and the first steps of patient evaluation for IV tPA therapy. Members of our stroke team (both faculty and fellows) rotate on “first call” to immediately answer the beeper 24 hours a day, 7 days a week. We have developed a code system that notifies other team members when the call is answered and there is always a backup person available if the code does not appear within 5 minutes of the initial page to the beeper. A brief “data card” is completed after each call listing patient demographics, intervals, and other critical information pertaining to IV tPA therapy eligibility. If the patient seems to be a valid candidate for IV tPA therapy, the stroke team member answering the page immediately goes to the ED to work with the ED medical and nursing staff and neurology resident (if available) in evaluating and treating the patient. At the 3 community hospitals, stroke team care is confined only to those patients who are candidates for IV tPA therapy and ends when the patient is discharged from the ED. Subsequent care is assumed by the private neurologist at our university hospital, all stroke patients, whether or not they receive IV tPA therapy, are admitted to the stroke service also managed by our stroke team. Starting in July 1, 1996, all stroke patients admitted to the stroke service at the university hospital have been entered into a stroke “log book” containing essential demographic and clinical information.

Prospective data for all consecutive patients treated with IV tPA at all 4 EDs over the 4 years of this analysis were collected from the data cards and at our university hospital, from the admission log book. This information included demographic variables, various intervals, stroke type, and in most cases, stroke severity at onset (the National Institutes of Health Stroke Scale [NIHSS] scores). Data collected by medical record review on all prospectively identified IV tPA-treated patients included protocol violations, NIHSS scores at 24 hours and at discharge, and hemorrhagic complications. When not documented, an NIHSS score was obtained by inference using clinical data in the stroke team medical record notes according to published validated guidelines. Symptomatic ICHs were determined by the presence of any intracerebral blood on follow-up head computed tomography or magnetic resonance imaging associated with an NIHSS score increase of 4 points or more. We calculated the rate of ICH based on all patients and on those patients who had follow-up radiological imaging. Mortality was determined as death during the hospital stay.

Stroke pathogenic mechanism was determined by medical record review of all prospectively identified IV tPA-treated patients following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. At our university hospital, a standard diagnostic workup was completed including carotid and cardiac ultrasound, electrocardiogram, and magnetic resonance imaging or follow-up computed tomography. At 3 community hospitals, the stroke pathogenic mechanism was determined from the information available in the ED similar to the NINDS rt-PA Stroke Study Group definitions. Telephone interview was used for long-term follow-up evaluation to determine long-term mortality.

We used SPSS for Windows (SPSS, Chicago, Ill) for statistical analyses. \( \chi^2 \) Test was used to assess any differences in variables between the hospitals.

were comparable to those of the NINDS rt-PA Stroke Study Group. Since that article was published, other studies have confirmed that IV tPA therapy can lead to benefit sustained at 1 year and that the rate of hemorrhagic complications with tPA therapy can be lower than initially reported by the Standard Treatment with Alteplase to Reverse Stroke (STARS) study and the NINDS rt-PA Stroke Study Group. However, other studies have pointed out higher rates of intracerebral hemorrhage (ICH) in community hospitals. Also, to our knowledge, there have been no published reports of higher rates of treatment with IV tPA than what we reported the NINDS rt-PA Stroke Study Group. However, in brief, a dedicated stroke beeper is carried by all fellows and faculty who constitute our stroke team. The beeper number is only available to the City of Houston Fire Department Emergency Medical Services (HFD-EMS) paramedics and the emergency department (ED) triage nurses of our 4 participating hospitals. Paramedics and ED nurses are regularly in-service to emphasize early and accurate recognition of patients with acute stroke and to institute an acute stroke management pathway that includes immediate notification of our stroke team and the first steps of patient evaluation for IV tPA therapy. Members of our stroke team (both faculty and fellows) rotate on “first call” to immediately answer the beeper 24 hours a day, 7 days a week. We have developed a code system that notifies other team members when the call is answered and there is always a backup person available if the code does not appear within 5 minutes of the initial page to the beeper. A brief “data card” is completed after each call listing patient demographics, intervals, and other critical information pertaining to IV tPA therapy eligibility. If the patient seems to be a valid candidate for IV tPA therapy, the stroke team member answering the page immediately goes to the ED to work with the ED medical and nursing staff and neurology resident (if available) in evaluating and treating the patient. At the 3 community hospitals, stroke team care is confined only to those patients who are candidates for IV tPA therapy and ends when the patient is discharged from the ED. Subsequent care is assumed by the private neurologist at our university hospital, all stroke patients, whether or not they receive IV tPA therapy, are admitted to the stroke service also managed by our stroke team. Starting in July 1, 1996, all stroke patients admitted to the stroke service at the university hospital have been entered into a stroke “log book” containing essential demographic and clinical information.

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We used SPSS for Windows (SPSS, Chicago, Ill) for statistical analyses. \( \chi^2 \) Test was used to assess any differences in variables between the hospitals.

A total of 269 patients were treated with 0.9 mg/kg of IV + PA at all 4 EDs covered by our stroke team between January 1, 1996, and June 1, 2000 (Table 1). Mean age was 68 years (age range, 24–93 years); 48% were women. Pretreatment mean ± SD NIHSS score was 14.4 ± 6.1 points (median, 14 points; range, 4–33 points). Pretreatment systolic blood pressure was 154 ± 28 mm Hg (mean ± SD). An IV tPA bolus was given at a median time of 137 minutes (range, 10–129 minutes) with 28% of the patients being treated within 2 hours. Mean door-to-needle time for all patients was 70 minutes (range, 10–129 minutes); it was 68 ± 28 minutes at our university hospital. Stroke mechanism was determined as cardioembolic in 53% of the patients; large vessel disease in 30%; and small vessel disease in 6%; and 11% had no determined cause. These variables did not vary over the 4 years of our analysis; for instance, NIHSS scores averaged 12.7, 14.4, 14.6, and 15.1 each of the 4 years, respectively.

During the 4-year interval of this study, our stroke team was alerted on our dedicated beeper 1689 times. Therefore, we treated 16% of patients for whom we were called. During the 4-year interval following July 1, 1996, a total of 1757 patients with symptoms of cerebral ischemia (including ischemic stroke, transient ischemic attack, and cerebral venous thrombosis) were admitted to
the stroke service at our university hospital, and 152 were treated with IV tPA according to the NINDS protocol. During this 4-year interval, incomplete data on total stroke admissions were available for 5 (nonconsecutive) months, and for those months, the monthly average for the previous 6 and following 6 months was used. Therefore, 8.7% of all patients presenting with symptoms of cerebral ischemia were treated over the 4-year period. The percentage and total number of patients treated increased each year (Figure). Over the final 6 months of our analysis, 12.9% of patients admitted with symptoms of cerebral ischemia were treated. Over the same interval, 14.7% of patients admitted with the diagnosis of acute ischemic stroke were treated.

Thirteen percent of the patients treated with IV tPA had protocol violations. This number did not vary over the 4 years of this analysis; the yearly protocol violation rates were 13.7%, 13.1%, 12.8%, and 13.1%, respectively. The most frequent violations in order of their occurrence were excessive blood pressure, seizure at onset, and high blood glucose level.

Symptomatic ICH occurred in 12 patients treated with IV tPA (Table 2). The overall symptomatic ICH rate was 5.6% (range, 3.6%-9.1%) between hospitals limiting analysis only to those with follow-up radiological imaging. The overall rate was 4.5% of all treated patients. A decline was noted from 1996 to 2000 (Figure B). Symptomatic ICH rate in treated patients with follow-up imaging who had protocol violations was 15% (also 15% of all treated patients who had protocol violations).

At 24 hours, the NIHSS score was 9.8±8.4 points (median, 8 points; range, 0-36 points). The mean±SD length of hospital stay was 9±5.7 days. In-hospital mortality was 15% and the discharge NIHSS score was 6.6±6.9 points (median, 3 points; range, 0-35 points). Patient disposition included: home, 33%; rehabilitation, 47%; and skilled nursing or other specialized facilities, 20%.

Follow-up was obtained in 123 patients, range 1 to 48 months (mean±SD, 19±13 months). Mortality following discharge was 17.8%.

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**Table 1. Patient Characteristics at Baseline, 24 Hours, and Discharge**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.7±13.4</td>
<td>24</td>
<td>93</td>
</tr>
<tr>
<td>NIHSS score, points</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>14.4±61</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>At 24 hours</td>
<td>9.8±8.4</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>At discharge</td>
<td>6.6±6.9</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Door-to-needle IV tPA therapy, min</td>
<td>70±28</td>
<td>10</td>
<td>129</td>
</tr>
<tr>
<td>Onset-to-bolus median, min</td>
<td>137±NA</td>
<td>30</td>
<td>180</td>
</tr>
<tr>
<td>Glucose level, g/dL†</td>
<td>146±81</td>
<td>65</td>
<td>633</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>154±28</td>
<td>75</td>
<td>253</td>
</tr>
<tr>
<td>LOS, d</td>
<td>9.0±5.7</td>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>

*NIHSS indicates National Institutes of Health Stroke Scale; IV tPA, intravenous tissue-type plasminogen activator; NA, does not apply; SBP, systolic blood pressure; and LOS, length of hospital stay.

†To convert the glucose level to Système International units of millimoles per liter, multiply by 0.05551.

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**Table 2. Symptomatic Intracerebral Hemorrhage (ICH) Rates in All Patients and Those With Second Computed Tomographic (CT) or Magnetic Resonance Imaging (MRI) Brain Scans at Each of the 4 Hospitals**

<table>
<thead>
<tr>
<th>Type of Hospital</th>
<th>All Treated Patients</th>
<th>All Second CTs or MRIs</th>
<th>All Symptomatic ICHs</th>
</tr>
</thead>
<tbody>
<tr>
<td>University</td>
<td>166</td>
<td>128</td>
<td>6</td>
</tr>
<tr>
<td>Community 1</td>
<td>46</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Community 2</td>
<td>39</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Community 3</td>
<td>18</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>269</td>
<td>213</td>
<td>12</td>
</tr>
</tbody>
</table>

A. The percentage of patients admitted to the stroke service at the university hospital with symptoms of cerebral ischemia who were treated with 0.9 mg/kg of intravenous tissue-type plasminogen activator. Data are averaged over 6-month intervals over the 4 years of the study. B. Total numbers of patients treated with 0.9 mg/kg of intravenous tissue-type plasminogen activator without symptomatic intracerebral hemorrhage (ICH) and total numbers and percentages of treated patients with symptomatic ICH at all 4 hospitals each year over the 4 years of the study. Asterisk indicates that the span of time is from January 1, 1996, through May 31, 1997. All other 4-year spans are from June 1 through May 31.

**Comment**

This large single-center experience shows that up to 15% of ischemic stroke patients can be treated with IV tPA and that the rate of symptomatic ICH can be lower than reported by the NINDS rt-PA Stroke Study Group,1 confirming other postmarketing studies.6,7

Our center is not typical of most hospitals taking care of stroke patients who might qualify for IV tPA therapy. However, with appropriate experience and organization, there is no reason why our data cannot be replicated or improved by other stroke centers. Perhaps the most notable unique characteristic of our experience is the large number of patients treated. We believe...
this is mainly due to the long-standing cooperation between our stroke team and the HFD-EMS that is responsible for approximately 80% of the ambulance transfers in the catchment area of our hospitals. Since the HFD-EMS recognizes our university hospital ED and stroke team as actively promoting stroke research, collaborative, and always available, they may preferentially triage appropriate IV tPA therapy candidates there. In 2000, a survey of all HFD-EMS stroke patient transports to all 4 of our hospitals showed that 47% of patients arrived within 2 hours of the onset of stroke symptoms. In 1999, 46.2% of all stroke patients in the city of Houston transported by the HFD-EMS were brought to 1 of our 4 hospitals. Our university hospital receives the largest proportion of stroke patients from the HFD-EMS of any single hospital in the city (18.5%).

Our calculation of percentage of treated patients is almost certainly inexact. We kept accurate records of whenever the stroke beeper was activated and found that we treated 16% of the patients for whom we were called, or roughly 1 of every 6 calls. We did not keep an accurate record of all stroke admissions to our community hospitals. We used a noncomputerized database of admissions to our university hospital stroke service that only differentiated between patients presenting with hemorrhagic vs ischemic symptoms based on admission clinical profile and brain imaging. Furthermore, complete data on total admissions were missing for 5 months scattered over the 4 years of our study. Among those with ischemic symptoms were included patients with transient ischemic attack, venous thrombosis as well as completed stroke, and also included elective admissions (roughly 10%) as well as those admitted through the ED. Based on these considerations and the fact that virtually all stroke patients admitted at that hospital were admitted to our stroke service, we are confident that our calculations, if anything, underestimate the percentage of true emergency stroke patients whom we treated. When we retrospectively reviewed our admission log, selecting only those patients presenting to the ED with the diagnosis of ischemic stroke, the percentage treated rose to 15%. Since the percentage treated rose steadily over the 4 years of our study, and was 13% to 15% (depending on whether we use the most conservative or more liberal denominator) over the final 6 months of our study, we believe that a 15% treatment rate (of patients presenting to the ED with ischemic stroke) is a realistic treatment target for stroke centers.

These calculations have important implications. They demonstrate that nationwide, and in our own center, we could be treating more patients than we currently do, since 85% to 87% are not being treated even in our own center. Thoughtfully conceived and appropriately targeted public and professional educational efforts may improve these numbers.12 Though these approaches have not been universally effective in improving ED arrival times or treatment rates in patients with acute myocardial infarction,13 it is possible that there is a greater void in knowledge among the public and emergency physicians regarding stroke that might be ameliorated by such educational efforts. Furthermore, establishment of stroke centers may help in directing patients to EDs where the expertise exists to treat larger numbers of patients.13 Another implication of our calculations is the need for maintaining a computerized database among active stroke centers so that an accurate record can be maintained of treatment rates and outcomes.

We found an overall low rate of symptomatic ICH with a nonsignificant trend toward a decline in hemorrhage rates from 1996 to 2000. We have no explanation for the possible decline in ICH rates since patient demographics, including NIHSS score and protocol violations, both of which are positively associated with higher rates of ICH,5,15 were similar from year to year. It is possible that the declining trend simply reflects yearly variability owing to the few patients with ICH each year.

There were no significant differences in the hemorrhagic complications between the university hospital and community hospitals served by our stroke team. This finding indicates that the presence of an experienced stroke treatment team is more important than the type of hospital itself in avoiding hemorrhagic complications of IV tPA therapy.

Overall patient baseline characteristics were similar between our study and the NINDS rt-PA Stroke Study Group (mean stroke severity of 14 points) and our patients had slightly more severe symptoms before treatment than in the European Cooperative Acute Stroke Study16,17 and the Cologne1 study. Therefore, our good results cannot be explained by less stringent criteria for treatment or by treating less severely affected patients. Only 6% of our treated patients had lacunar stroke. This is fewer than the number of patients with small vessel disease in other studies.18-20 The low prevalence of lacunar stroke and high prevalence of cardioembolic stroke in our patient population may have affected the recovery and mortality rates seen in our study, if there is anything negatively biasing our results.

The higher rate of ICH in patients with NIHSS protocol violations was once again confirmed by our study, underscoring the need to adhere to published guidelines to use IV tPA therapy safely in stroke patients. The most common protocol violation in our study was elevated blood pressure at the time of treatment. Most other reviews have found that treatment beyond the 3-hour window of time was a common violation. During most of this study at our university hospital, where most of our patients were treated, we had an investigational protocol for treatment of patients beyond 3 hours with lower dose IV tPA therapy (these patients and others treated with investigational protocols were not counted among the treated patients in this analysis). Therefore, there was no pressure on the treating physician to "bend the rules" to use conventional dose IV tPA therapy if the patient could not be treated within 3 hours. This probably accounts for why treatment beyond 3 hours was not a common protocol violation in this series.

It is possible that our data collection method resulted in an underestimate of the number of symptomatic hemorrhages. Though all patients and most hemorrhages were identified prospectively, the incidence of ICH was determined in part by medical record review. Although physician and nursing notes were carefully scrutinized for any evidence of deterioration in the patient’s condition and all follow-up computed tomography and magnetic resonance imaging scan reports were reviewed, it is possible that some cases of ICH were missed.
since 56 patients (21%) did not have follow-up scans. To be conservative, hemorrhage rates were calculated based only on those patients with medical records and follow-up radiological imaging available for review. This rate (5.6%) was not significantly different than the rate if all patients were included in the calculation (4.5%). We surmise that the true symptomatic ICH rate is closer to 4.5% than 5.6% in our patient population assuming that those patients whose physicians did not believe it necessary to repeat brain imaging were not likely to have had a symptomatic hemorrhage. Furthermore, all of our patients who died had follow-up imaging prior to death.

Outcome can be affected by the time from symptom onset to initiation of IV tPA therapy. In our patients, the median time from stroke onset to tPA bolus was 137 minutes (range, 30-180 minutes) with 28% of patients treated within 2 hours from stroke onset. In the NINDS rt-PA Stroke Study Group, more than 50% of the patients were treated within 90 minutes from stroke onset. The average door-to-needle time in our study was 70 minutes (68 minutes in our university hospital), better than in our previous report of our first year’s experience (100 minutes) and 96 minutes reported in the Standard Treatment with Alteplase to Reverse Stroke study. Nevertheless, this time is still longer than published goals (60 minutes). In our experience, most delays in treatment initiation are attributable to determination of international normalized ratio in patients previously receiving coumadin therapy, location of patient relatives or witnesses to determine the time of onset, and availability of the computed tomography scanner when major trauma victims are being concurrently evaluated. Therefore, the use of fingerstick international normalized ratio screening, cooperation with paramedic personnel to determine onset time, and better coordination of radiological imaging tests may further improve the door-to-needle time.

An experienced and well-organized stroke center can safely and effectively treat up to 15% of ischemic stroke patients with IV tPA, but successful results depend on adherence to published guidelines.

Accepted for publication August 1, 2001.

This investigation was supported by National Institutes of Health fellowship training grant T32 NS07412 to the University of Texas–Houston Stroke Program (Dr Burgin); a postdoctorate grant from the Egyptian Ministry of Higher Education as an assistant lecturer in the Department of Neurology, Mansoura University (Dr El-Mitwalli); and a Summer Student Training Stipend (Ms Long).

We recognize the medical and nursing staffs of the Memorial Hermann Hospital Emergency Department and Stroke Unit, the nursing staffs of the Memorial Southwest, Memorial Northwest, and the St Luke’s Episcopal Hospital Emergency Departments, and the City of Houston Fire Department Emergency Medical Services for their collaboration in the efforts of our stroke team.

We also acknowledge the assistance of the present and former stroke team fellows who helped manage these patients: Fahmi Al-Senani, MD, David Chiu, MD, Andrew Demchuk, MD, Neeraj Dubey, MD, Robert Felberg, MD, Susan Hickenbottom, MD, Scott Kasner, MD, Nicholas Okon, DO, Paisith Piriyawat, MD, Carlos Villar-Cordoba, MD, and Theodore Wein, MD.

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