Outcomes of Treatment with Recombinant Tissue Plasminogen Activator in Patients Age 80 Years and Older Presenting with Acute Ischemic Stroke

Jennifer C. Drost, DO, MPH, and Susana M. Bowling, MD

ABSTRACT

• **Background:** Ischemic stroke is a major cause of morbidity and mortality for patients ≥ 80 years old. The use of intravenous recombinant tissue plasminogen activator (tPA) in patients ≥ 80 years for treatment of ischemic stroke remains controversial.

• **Objective:** To examine outcomes in patients ≥ 80 years old who received tPA in our institution.

• **Methods:** This was a retrospective cohort study at a community-based certified acute stroke center. Individuals age ≥ 80 years evaluated emergently for acute neurologic changes consistent with ischemic stroke were included (n = 184). The comparison groups within this sample were patients who received tPA versus those who did not because they came to the ED outside of the treatment window. Outcome measures included length of stay, symptomatic intracerebral hemorrhage (ICH), discharge disposition, and in-hospital death.

• **Results:** 38 patients (20.7%) received tPA. 50 patients (27.2%) presented outside of treatment windows and were included in comparative analysis. There was no difference between groups in age (P = 0.26) or initial National Institute of Health Stroke Scale (P = 0.598). One patient (2.6%) who received tPA developed symptomatic ICH. Those receiving tPA were more likely to be discharged to acute rehabilitation hospitals (P = 0.012) and less likely to experience in hospital death (P = 0.048).

• **Conclusion:** At this institution, the use of tPA in patients ≥ 80 years old is not associated with increased mortality or risk of symptomatic ICH. Those who received tPA were more likely to be discharged to acute rehabilitation hospitals, suggesting greater potential for functional recovery.
Outcomes of tPA

Methods

The study setting was a 540-bed acute care hospital that is a community-based certified stroke center. This study was deemed nonhuman subjects research by the institutional review board as the goal was to evaluate processes and outcomes of this institution's stroke team in treating a subgroup of patients according to clinically accepted practice (quality improvement initiative). All patients presenting to the emergency department (ED) between 1 January 2011 and 30 November 2013 with the onset of stroke-like neurological deficits underwent evaluation and treatment by a neurologist and/or specially trained stroke team. This team consists of the attending neurologist, ED physician, resident physicians, advanced practice nurses, and ED staff nurses and emergency medicine technicians. Team members involved in the evaluation and treatment of these patients undergo routine clinical education and testing to ensure standardization. Patients undergo emergent evaluation including the National Institutes of Health Stroke Scale (NIHSS) and obtain brain imaging with computed tomography (CT).

Patients ≥ 80 years were identified among all those who presented to the ED with ischemic stroke. Patients were included if they were subsequently diagnosed with ischemic stroke or transient ischemic attacks (TIA). They were excluded from analysis if neurological changes were due to primary hemorrhagic stroke, intracranial hemorrhage, subarachnoid hemorrhage, seizure, conversion disorder, or metabolic derangements. They were also excluded from analysis if the acute ischemic stroke treatment included intra-arterial administration of tPA or endovascular revascularization.

Patient data collected included age, NIHSS at presentation to ED, time to presentation at ED, treatment with tPA, contraindications to tPA, discharge disposition, length of stay and in-hospital mortality. Raw NIHSS values were collected at the time of presentation. NIHSS were categorized into mild symptoms (NIHSS < 6), moderate symptoms (NIHSS 6–19), or severe symptoms (NIHSS ≥ 20). Clinical indications for receiving tPA include NIHSS > 4, focal neurological deficit onset < 3 hours (for those ≥ 80 years old), and no evidence of acute hemorrhage or acute infarct on CT. Contraindications include rapidly improving symptoms (repeat NIHSS < 4), active or history of intracranial hemorrhage, history of stroke or head trauma in past 3 months, gastrointestinal or genitourinary hemorrhage within 21 days, major surgery within 14 days, arterial puncture at a noncompressible site in past 7 days, treatment with anticoagulation with therapeutic indices, systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg and not responding to treatment, or platelet count < 100,000/mm³. Patients who were not eligible for tPA based on contraindications with the exception of being outside the treatment window (3 hours) were excluded from comparative analysis. Patient length of stay was rounded to nearest full day. Discharge disposition was categorized as home, acute rehabilitation hospital, skilled nursing facility, home or facility with hospice services, other hospital setting, or death.

Statistics were calculated using SPSS statistical software. Variables were reported as means and percentages. Group means were compared using t tests and differences in proportions were compared using the chi square test. Correlations were performed using Pearson’s correlation. A 2-tailed P < 0.05 was considered statistically significant.

Results

From 1 January 2011 to 30 November 2013, a total of 984 people presented to the ED with acute neurological changes concerning for ischemic stroke. Of those, 184 people (18.7%) were 80 years or older with an average age of 85.3 (range, 80–96). Patient characteristics are presented in Table 1. The average NIHSS was 12 (range, 1–32). Thirty-four (18.5%) patients presented with severe stroke symptoms (NIHSS ≥ 20), while moderate symptoms (NIHSS 6–19) and mild symptoms (NIHSS < 6)
accounted for 97 (52.7%) and 52 (28%) cases, respectively. Age and presenting NIHSS were positively correlated ($P = 0.002$). The overall in-hospital mortality rate for the population was 23.4%. Those with presenting NIHSS $> 20$ were more likely to experience in-hospital death ($P < 0.001$).

Thirty-eight patients (20.7%) received tPA and had an average age of 84.8 years, while 146 (79.3%) did not receive tPA and had an average age of 85.4 years. Of those that did not receive tPA, 128 (87.7%) had 1 or more clearly documented contraindications (Table 2). Ten patients (6.8%) were excluded due to clinical concerns including comorbidities, debility, or advanced dementia. Fifty-three (36.3%) of patients had rapidly improving stroke symptoms with repeat NIHSS < 4. Of those with contraindications, 49 (33.6%) had arrival outside the 3-hour treatment window, unknown time of onset, or developing radiographic changes on CT representing the natural history of stroke progression. Fourteen (9.6%) were on anticoagulants including warfarin and dabigatran with elevated INR or thrombocytopenia. Seven (4.8%) had a history of intracranial hemorrhages and 11 (7.5%) had recent surgery or bleeding episodes. Only 8 (5.5%) patients declined treatment with tPA.

Those with contraindications including rapidly improving symptoms, treatment with anticoagulants with therapeutic indices, recent bleeding episodes, or family refusal were excluded from comparative analyses. The remaining 50 patients were included in comparative analysis (Table 3). There was no difference between the tPA and non-tPA groups in age ($P = 0.26$). While overall there was no difference between groups in initial NIHSS ($P = 0.598$), more patients with moderate symptoms (NIHSS 6-19) received tPA ($P = 0.023$). Similarly, those who did not receive tPA were more likely to have presented with mild or severe symptoms ($P = 0.023$). There was no significant difference in length of stay between the tPA group (6.4 days) and non-tPA group (5.8 days) ($P = 0.606$). Sixteen (42.1%) patients who received tPA were discharged to acute rehabilitation hospitals, compared to 7 (14%) of those that did not receive tPA ($P = 0.003$). There was no difference between groups in the numbers discharged to home ($P = 0.40$) or to skilled nursing facilities ($P = 0.121$). Those who receive tPA were less likely to experience in hospital death ($P = 0.048$). Only 1 patient (2.6%) who received tPA, versus zero who did not receive tPA, developed symptomatic ICH ($P = 0.249$).

**DISCUSSION**

Ischemic stroke remains a major cause of morbidity and mortality for very old patients. Though less than 5% of the United State population is over the age of 80 [1], at this community-based hospital 18% of those presenting to the ED with ischemic stroke were in this age-group. With a population of increasing age, more people in this age-group will present with ischemic stroke and need effective treatment to limit the associated morbidity and mortality. Being able to quickly and safely treat acute ischemic stroke may help very old adults maintain independence or prevent institutionalization. While the original studies demonstrating the effectiveness of tPA for acute ischemic stroke excluded or underrepresented those $\geq 80$ years, retrospective analysis has not been conclusive regarding its use in very old patients [4–6,10,12,13]. However,

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**Table 1. Patient Characteristics ($n = 184$)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>85.3</td>
</tr>
<tr>
<td>Mean NIHSS (range)</td>
<td>12 (1–32)</td>
</tr>
<tr>
<td>NIHSS &lt; 6, $n$ (%)</td>
<td>52 (28)</td>
</tr>
<tr>
<td>NIHSS 6–19, $n$ (%)</td>
<td>97 (52.7)</td>
</tr>
<tr>
<td>NIHSS $\geq$ 20, $n$ (%)</td>
<td>34 (18.5)</td>
</tr>
<tr>
<td>Length of stay in days (range)</td>
<td>5.3 (0–30)</td>
</tr>
<tr>
<td>Received tPA, $n$ (%)</td>
<td>38 (20.7)</td>
</tr>
<tr>
<td>Mortality/in-hospital death, $n$ (%)</td>
<td>43 (23.4)</td>
</tr>
</tbody>
</table>

**Table 2. Contraindications to Receiving tPA**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>$n$</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly improving symptoms/repeat NIHSS &lt; 4</td>
<td>128</td>
<td>87.7</td>
</tr>
<tr>
<td>Neurological deficit onset &gt; 3 hours/unknown onset time</td>
<td>41</td>
<td>28.1</td>
</tr>
<tr>
<td>CT changes showing evidence of acute infarct or acute hemorrhage</td>
<td>19</td>
<td>13.0</td>
</tr>
<tr>
<td>Antiocoagulants/INR $&gt; 1.7$, thrombocytopenia</td>
<td>14</td>
<td>9.6</td>
</tr>
<tr>
<td>Recent surgery or GI/GU bleeding</td>
<td>11</td>
<td>7.5</td>
</tr>
<tr>
<td>History of stroke or head trauma $&lt; 3$ months</td>
<td>9</td>
<td>6.1</td>
</tr>
<tr>
<td>History or presence of intracranial or subarachnoid hemorrhage</td>
<td>7</td>
<td>4.8</td>
</tr>
<tr>
<td>Patient or family refusal of treatment</td>
<td>8</td>
<td>5.5</td>
</tr>
</tbody>
</table>
post-hoc analysis of NINDS and IST-3 data demonstrate efficacy and safety of treatment [12,13].

This study explored the use of tPA at a community-based certified stroke center. Similar to previous studies, it demonstrates the large proportion of patients presenting with acute neurological findings consistent with ischemic stroke are ≥ 80 years old [3,6]. Our incidence of acute ischemic stroke in the oldest patients may be slightly lower than reported elsewhere, which may reflect community differences, with higher rates of younger patients with multiple comorbidities presenting with stroke-like symptoms. Amongst this very old cohort, age was positively correlated with stroke severity. Mortality in patients ≥ 80 years old who present with acute ischemic stroke approaches 25%.

The majority of patients who did not receive tPA had documented contraindications to receiving the medication. The most common reason was rapidly improving symptoms with repeat NIHSS often ≤ 4. The second most common reason was presentation outside the treatment window of 3 hours. We compared those who either arrived too late to receive treatment with tPA or already had ischemic changes on CT to those who received tPA as this suggests the natural history of stroke progression and outcome without effective, early treatment. The outcomes at this institution support this trend. Very old patients who received tPA did not experience harm as evidenced by similar lengths of stay and rates of discharge to home. Also, rates of symptomatic ICH were lower than those reported in the literature. In fact, patients who received tPA were less likely to experience in-hospital death and more likely to be discharged to acute rehabilitation hospitals, suggesting more functional ability to tolerate aggressive recovery efforts.

Very few people who presented with acute ischemic stroke and were eligible for treatment with tPA failed to receive it. This suggests that despite the perceived increased risk to treating these patients with tPA, the specialized stroke team aggressively treats patients age ≥ 80 years who present with acute ischemic stroke. However, those who did not receive tPA were more likely to have presented with mild or severe strokes. This may suggest that treatment time frames are more strongly held, or that treatment teams are more likely to use time frames as a reason to not treat with tPA for patients with mild or severe strokes. Also, very few patients and families who were eligible to receive tPA declined treatment despite the associated risks. This suggests that patients and families are eager for aggressive treatment in attempt to prevent death or disability associated with ischemic stroke.

There are several limitations associated with this evaluation. First, this is a retrospective analysis of a single institution’s acute stroke procedures. Data was collected in an effort to evaluate the processes and outcomes of the specialized stroke team in evaluating and treating this very old cohort who present to a community-based hospital. It involved individualized clinical evaluation and decision making by multiple care providers who may offer different perspectives on the risk of treating patients ≥ 80 years old with tPA, which may result in selection bias. While comparing those who arrived outside treatment windows offers a comparison group who represents the natural course of untreated strokes, patient characteristics that prevented timely evaluation may also impact their outcomes including baseline mobility, care giving availability and underlying medical comorbidities. The similarity in mean presenting NIHSS scores of the two groups, however, argues against this possibility. Lastly, exclusion criteria to receiving tPA may represent intrinsic characteristics that impart higher risk of negative outcomes.

**Conclusion**

Although there have been no randomized controlled trials that evaluate the safety and efficacy of tPA in the treatment of acute ischemic stroke in very old patients, use at the community-based stroke center was not as-
associated with worse outcomes including symptomatic ICH, hospital length of stay, and in-hospital mortality. In fact, there were trends towards better outcomes in older patients who received tPA, including a significant reduction in in-hospital mortality. This evaluation supports the benefits of using tPA to treat acute ischemic stroke as seen in prior randomized controlled trials that included the treatment of very old patients. Though ongoing research is needed, a growing body of evidence supports the use of tPA to treat acute ischemic stroke in patients ≥ 80 years.

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REFERENCES


