Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in Patients Aged 80 Years and Older

The tPA Stroke Survey Experience

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Background and Purpose—Intravenous tissue plasminogen activator (tPA) administered within 3 hours of symptom onset is the first available effective therapy for acute ischemic stroke (AIS). Few data exist, however, on its use in very elderly patients. We examined the characteristics, complications, and short-term outcome of AIS patients aged ≥80 years treated with tPA.

Methods—Patients aged ≥80 years (n=30) were compared with counterparts aged <80 years (n=159) included in the tPA Stroke Survey, a US retrospective survey of 189 consecutive AIS patients treated with intravenous tPA at 13 hospitals.

Results—Risk of intracerebral hemorrhage (fatal, symptomatic, and total) was 3%, 3%, and 7% in the elderly age group and 2%, 6%, and 9%, respectively, in their younger counterparts (P=NS for all comparisons). Likelihood of favorable outcome, defined as modified Rankin score 0 to 1, National Institutes of Health Stroke Scale score ≤5, or marked improvement by hospital discharge, was comparable between groups (37%, 54%, and 43% versus 30%, 54%, and 43%, respectively; P=NS for all comparisons). Elderly patients were more likely to be treated by stroke specialists (87% versus 60%; P=0.005) and less likely to have an identified protocol deviation (13% versus 33%; P=0.03). Elderly patients were discharged more often to nursing care facilities (17% versus 5%; P=0.003). In logistic regression models there were no differences in odds ratio for favorable or poor outcome, other than tendency for higher in-hospital mortality in elderly patients (odds ratio, 2.8; 95% CI, 0.81 to 9.62; P=0.10).

Conclusions—Among AIS patients treated with intravenous tPA, age-related differences in characteristics and disposition were identified. No evidence for withholding tPA treatment for AIS in appropriately selected patients aged ≥80 years was identified. (Stroke. 2000;31:370-375.)

Key Words: cerebral ischemia • elderly • stroke • thrombolytic therapy

The treatment of elderly patients who sustain an acute ischemic stroke (AIS) presents physicians with a unique and increasingly important challenge. The risk of stroke, the leading cause of severe disability, increases exponentially with age.1–4 Life expectancy has increased over the past few generations, and the proportion of elderly in the western population is expected to further increase.5,6 Elderly AIS patients aged ≥80 years are, however, often excluded or underrepresented in clinical trials for AIS.7–9

Intravenous tissue plasminogen activator (tPA) administered within 3 hours of symptom onset is a proven effective therapy for AIS.10–12 Few data are available on its use in the very old. The purpose of this study was to compare the characteristics, complications, and in-hospital outcome of AIS patients aged ≥80 years treated with intravenous tPA with their younger counterparts in a series of patients treated in routine clinical practice.

Subjects and Methods

All analyses are based on data obtained in the multicenter tPA Stroke Survey.13 Hospitals within several selected cities with an organized stroke triage system and experience with the use of intravenous tPA for AIS per published protocols10,12 were retrospectively surveyed.

Investigators at each hospital reviewed records of consecutive patients treated with tPA after the publication of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Trial results10 and up to no later than December 1997. Sources of information for data extraction included prehospital emergency medical services, emergency department, radiology, and inpatient...
medical records. Patient demographics, medical history, stroke severity, CT scans, adherence to the NINDS rtPA Stroke Trial protocol, complications attributable to tPA, and in-hospital outcome were evaluated. A standardized form was used to systematically collect data.

Three measures of patient outcome and clinical course at discharge were assessed. Pretreatment and discharge National Institutes of Health Stroke Scale (NIHSS) scores, measuring neurological impairment, were reported categorically in 5-point intervals (≤5, 6 to 10, 11 to 15, 16 to 20, or >20), similar to the categorization in the NINDS rtPA Stroke Trial. The modified Rankin Scale was used to assess disability at discharge categorized as no significant disability (score 0 to 1), mild to moderate disability but able to walk (score 2 to 3), and moderate to severe disability and unable to walk (score 4 to 5). Both NIHSS and the modified Rankin Scale categories were estimated by the local investigators from the medical records, unless available as part of the routine treatment protocol. Finally, the local investigator also determined a subjective assessment of the in-hospital clinical course for each patient. This categorized the clinical course from presentation to discharge as in-hospital death, deteriorated, stable (no change), mildly improved, or markedly improved.

Treat ing physicians were categorized into stroke specialists versus other physicians (neurologists, emergency physicians, or others) by each local investigator. The definition used to determine a stroke specialist was participation in a fellowship training and/or devotion of the majority of clinical practice to stroke. Each local investigator retrospectively determined deviations from NINDS rtPA Stroke Trial treatment protocol guidelines. Protocol deviations were not assessed in a blinded fashion. Severe strokes or early ischemic changes on brain CT, not exclusion criteria in the NINDS rtPA Stroke Trial, were not regarded as deviations in this survey.

A central study neuroradiologist, using NINDS rtPA Stroke Trial criteria, reviewed any CT scans considered to have an intracerebral hemorrhage (ICH), including hemorrhagic infarction, parenchymal hematoma, and intraventricular or subarachnoid hemorrhage. ICH within 36 hours of tPA infusion was considered related to tPA administration. Symptomatic ICH was defined as a CT-documented hemorrhage that was judged to be temporally related to deterioration in the patient’s clinical condition, while fatal ICH was defined as a CT-documented hemorrhage associated with an in-hospital death. Asymptomatic ICH was defined as CT-documented hemorrhage identified on a routine follow-up without associated clinical deterioration.

Patients were stratified into 2 age groups: ≥80 years and <80 years. Baseline characteristics, complications, and in-hospital outcome were compared between groups.

### Statistical Analysis

Univariate comparisons were conducted with the Fisher exact test or the χ² test for dichotomous variables, Wilcoxon rank sum test for ordered categorical variables, and Student’s t test for normally distributed variables. Logistic regression models were performed to assess the role of age ≥80 years on outcome variables. Those variables differing between the age groups at the P < 0.20 critical level in the univariate analyses were included in the logistic regression models. Baseline stroke severity, a major predictor of outcome, was also included in the logistic regression model. All statistical analyses were performed with SAS version 6.12 software.

### Results

#### Clinical Characteristics

The age of the 189 patients ranged from 30 to 97 years. Baseline characteristics of elderly patients aged ≥80 years (n = 30) and their counterparts aged <80 years (n = 159) are shown in Table 1. No significant differences in sex, race, or stroke location or subtype were identified between groups. Elderly stroke patients were less likely to smoke cigarettes or have a history of diabetes mellitus (10% versus 26%; P = 0.05 for both variables) and were more likely to have a higher peak pretreatment systolic blood pressure. The elderly had a higher proportion of prior strokes, atrial fibrillation, and congestive heart failure and were more often on antithrombotic therapy, although these differences did not reach statistical significance. Distribution of baseline stroke severity categories was not significantly different between groups. Only 10% of elderly patients and 15% of those aged <80 years had an estimated NIHSS score > 20.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age &lt;80 y (n = 159)</th>
<th>Age ≥80 y (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>61 (30–79)</td>
<td>65 (80–97)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>100 (63%)</td>
<td>115 (50%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>109 (69%)</td>
<td>19 (63%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>40 (25%)</td>
<td>10 (33%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>10 (6%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>97 (61%)</td>
<td>21 (70%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42 (26%)</td>
<td>3 (10%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>42 (26%)</td>
<td>3 (10%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>24 (15%)</td>
<td>6 (20%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (19%)</td>
<td>7 (23%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>27 (17%)</td>
<td>7 (23%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>17 (11%)</td>
<td>0 (0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Antithrombotic therapy</td>
<td>52 (33%)</td>
<td>15 (50%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak pretreatment, mean SD mm Hg</td>
<td>162 ± 30</td>
<td>181 ± 29</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP</td>
<td>86 ± 18</td>
<td>85 ± 19</td>
<td>0.68</td>
</tr>
<tr>
<td>NIHSS scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>54 (34%)</td>
<td>11 (37%)</td>
<td></td>
</tr>
<tr>
<td>11–15</td>
<td>39 (25%)</td>
<td>8 (27%)</td>
<td></td>
</tr>
<tr>
<td>≥16</td>
<td>65 (41%)</td>
<td>11 (37%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Edema/mass effect on baseline CT</td>
<td>12 (8%)</td>
<td>2 (7%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Location: anterior circulation</td>
<td>141 (89%)</td>
<td>30 (100%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Subtype*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>65 (41%)</td>
<td>12 (41%)</td>
<td></td>
</tr>
<tr>
<td>Noncardioembolic</td>
<td>58 (36%)</td>
<td>9 (31%)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>36 (23%)</td>
<td>8 (28%)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Risk factors not noted in medical records were regarded as not present. Missing data are excluded from analysis. Values are expressed as number (percentage) unless otherwise indicated.

*Based on clinical data and in-hospital evaluation.

### Baseline Characteristics of Patients With Acute Ischemic Stroke Treated With tPA

#### TABLE 1.

have a history of diabetes mellitus (10% versus 26%; P = 0.05 for both variables) and were more likely to have a higher peak pretreatment systolic blood pressure. The elderly had a higher proportion of prior strokes, atrial fibrillation, and congestive heart failure and were more often on antithrombotic therapy, although these differences did not reach statistical significance. Distribution of baseline stroke severity categories was not significantly different between groups. Only 10% of elderly patients and 15% of those aged <80 years had an estimated NIHSS score >20.

Treating physicians were stroke specialists in 87% of elderly versus 60% of younger patients (P=0.005). The NINDS rtPA Stroke Trial inclusion/exclusion criteria were followed with greater accuracy in the elderly, with only 13% of treated elderly patients identified with a protocol deviation compared with 33% in younger patients (P=0.03). Specific deviations are summarized in Table 2.
In-Hospital Complications and Outcome

In-hospital outcomes and dispositions are summarized in the Figure. Proportion of favorable outcome at hospital discharge (modified Rankin Scale score 0 to 1) did not differ between groups (37% elderly versus 30% of younger patients; P = 0.52). At discharge, NIHSS scores ≤5 were noted in 54% and marked improvement in 43% of both groups (P = 0.99 for both). Elderly patients were less frequently discharged home compared with those aged <80 years (20% versus 46%, respectively) and were more often discharged to long-term nursing care facilities (17% versus 5%, respectively; P = 0.003). Proportions of poor outcome (modified Rankin Scale score 4 to 5), severe residual neurological deficit (NIHSS score ≥11), and deterioration from baseline were similar in both groups of patients. Median length of hospital stay was 9 days (range, 3 to 26 days) in elderly patients compared with 10 days in their younger counterparts (range, 1 to 84 days; P = 0.91).

Risk of symptomatic, fatal, or total ICH did not differ between patients aged ≥80 years and their younger counterparts (Table 2). Total ICH risk was 7% in patients aged ≥80 years and 9% in those aged <80 years. Risks, however, were not equally distributed between patients aged <80 years and increased from as low as 3% in patients aged ≥60 years to 14% and 15% in patients aged 60 to 70 and 70 to 80 years, respectively.

Mortality during the initial hospitalization was 2.5-fold higher among the elderly than among younger patients (20% versus 8%; P = 0.04), with underlying causes of deaths summarized in Table 2. All patients dying in-hospital had premorbid repeated brain imaging to determine whether they developed an ICH. Percentages do not always total 100 because of rounding. Deter indicates deterioration; rehab, rehabilitation.

Odds ratios for different outcome measures were calculated after adjustment for group differences in baseline characteristics and for baseline stroke severity, a major determinant of outcome (Table 3). The elderly had an approximately 3-fold (adjusted) increased risk of dying, although this difference did not reach statistical significance.
TABLE 3. Logistic Regression Models for Age ≥80 Years as Predictor of In-Hospital Outcome

<table>
<thead>
<tr>
<th>Predictor of In-Hospital Outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome (modified Rankin 0–1 at discharge)</td>
<td>1.3</td>
<td>0.50–3.62</td>
<td>0.56</td>
</tr>
<tr>
<td>Marked improvement (subjective physician’s assessment)</td>
<td>1.1</td>
<td>0.45–2.51</td>
<td>0.90</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>2.8</td>
<td>0.81–9.62</td>
<td>0.10</td>
</tr>
<tr>
<td>Poor outcome (in-hospital mortality or modified Rankin 4–5)</td>
<td>1.3</td>
<td>0.52–3.20</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Models are adjusted for baseline NIHSS score, pretreatment systolic blood pressure, diabetes mellitus, cigarette smoking, and use of antiplatelet medications.

statistical significance (95% CI, 0.81 to 9.62; P=0.10). No significant differences between groups were identified for reaching other outcome measures.

**Discussion**

Recent reports from the US Department of Commerce, Bureau of Statistics highlight the aging nature of the US population. The number of individuals aged ≥65 years is projected to increase from 39 million in 1995 to 69 million, or 20% of the total population, in 2030. The fastest growing age group will be the population aged ≥85 years, doubling its 1995 size of 3.6 million by 2025 and increasing 5-fold to 18.2 million individuals by 2050. Currently, men reaching 80 years of age can expect to live an additional 7 years, while women average an additional 9 years.

Stroke primarily affects an elderly population. Data from Rochester, Minn, demonstrated that more than half of the strokes in this population affected subjects aged ≥75 years and nearly one quarter affected subjects aged ≥85 years. Furthermore, elderly stroke patients are reported in population-based and hospital-based studies to have more severe strokes, the case-fatality rate is higher, and a larger proportion are discharged to long-term institutional care.

**ICH Related to tPA**

The main determinants of ICH in the NINDS rtPA Stroke Trial were stroke severity (as measured by the NIHSS) and early CT ischemic changes. Increasing age was not an independent predictor of symptomatic ICH in the NINDS rtPA Stroke Trial but emerged as a predictor for parenchymal hemorrhage in post hoc analysis in the European Cooperative Acute Stroke Study.

Several factors may theoretically increase the risk of ICH in elderly patients with AIS, including cerebral amyloid angiopathy, frail vasculature, and impaired rate of tPA clearance. These theoretical factors may partly explain why patients aged ≥80 years are often excluded or underrepresented in experimental therapy clinical stroke protocols. An age effect on risk of ICH was observed in our cohort aged <80 years, but the rate of ICH was not higher in those aged ≥80 years. These findings, although clearly preliminary, suggest no substantial excess risk from tPA therapy in selected patients aged ≥80 years. However, particular caution was exercised in selection of elderly patients for treatment in our cohort. Furthermore, treating physicians were more often stroke specialists, and the NINDS rtPA Stroke Trial inclusion/exclusion criteria were followed with greater accuracy in the elderly. Therefore, these findings should not be generalized to all elderly AIS patients in any circumstances.

**In-Hospital Outcome**

A trend for higher mortality was observed among elderly AIS patients treated with tPA in the present survey (adjusted odds ratio, 2.8; P=0.10). A large body of evidence has shown higher mortality rates in elderly AIS patients not treated with tPA. The increased mortality among elderly stroke patients was not explained by a higher risk of symptomatic ICH. Elderly stroke patients were also less likely to go home and more likely to be sent to nursing homes. The reasons for the higher risk of mortality and disposition to long-term nursing facilities in elderly stroke patients are not entirely clear. Higher immediate poststroke disability, patient’s preferences, lack of social support, and level of care provided may play a contributory role.

Proportions of favorable outcome and marked improvement were similar in the elderly and younger stroke patients, suggesting that beneficial effect from tPA may be of similar magnitude in elderly AIS patients. Indeed, no threshold value for age was identified in subgroup analysis of the NINDS rtPA Stroke Trial that precludes tPA treatment.

**Thrombolytic Therapy for Acute Myocardial Infarction in the Elderly**

Thrombolytic therapy was consistently found to be beneficial in elderly patients with acute myocardial infarction, although this patient group was also associated with higher mortality and higher rates of ICH. ICH occurred in 0.4% of patients aged <65 years, 1.2% of those aged 65 to 74 years, and 2.1% of those aged ≥75 years in the National Registry of Myocardial Infarction. Thrombolytic therapy was shown, on the basis of major myocardial infarction trials, to be cost-effective in the elderly, in addition to having clear net benefits.

**Study Limitations**

Analyses are derived from a retrospective survey and are thus limited by such methodology. In the absence of randomized trials specifically targeting elderly patients for AIS, observational data can, however, supplement our knowledge. The decision of whether to recommend tPA was at the discretion of the evaluating physician at each center. This potentially introduced bias, resulting in the selection of less severely ill elderly patients. Therefore, these results should not be generalized to elderly patients with severe strokes, severe comorbidities, or poor pre-stroke functional status. Furthermore, because of the limited sample size of elderly patients (mostly octogenarians) and the absence of long-term follow-up, the results should be confirmed in larger prospective studies.

**Conclusion**

In conclusion, these preliminary data suggest that the potential risks and benefits from intravenous tPA use in carefully selected...
elderly patients aged ≥80 years are of a magnitude comparable to those in younger stroke patients. Clinical decision making regarding treatment of elderly patients sustaining an AIS is complex and is likely to be influenced by medical comorbidities, patients’ preferences, and ethical and economic considerations. The option of this therapy, however, should not be categorically denied for appropriately selected elderly patients solely on the basis of their age, and such patients should be considered for treatment in future clinical trials.

Appendix

The tPA Stroke Survey Group


References


Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in Patients Aged 80 Years and Older: The tPA Stroke Survey Experience

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