Outcomes of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in Patients Aged 90 Years or Older

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Although age is a major risk factor for stroke, physicians are often reluctant to use thrombolytic agents in those who are very old. No published study provides detailed information on the use of intravenous tissue plasminogen activator (tPA) in patients aged 90 years or older. We retrospectively reviewed the use of intravenous tPA for patients 90 years or older who were admitted with acute ischemic stroke to the hospital at 4 academic centers from March 1, 1999, to March 1, 2008. We reviewed the clinical features of the patients at presentation, complications, and outcomes. Twenty-two patients (11 women; median age, 93 years; range, 90-101 years) were identified who had received intravenous tPA for symptoms of acute ischemic stroke (average time to treatment, 143 minutes; range, 90-180 minutes; no tPA protocol violations; mean National Institutes of Health Stroke Scale score, 15; range, 5-28). Nearly all patients were highly functional at baseline (median modified Rankin Scale [mRS] score, 1; median Barthel Index score, 95), and all but one performed the activities of daily living with little or no assistance before stroke. By the 30-day follow-up, 2 patients (9%) had a favorable outcome (mRS score, 0-2) and 2 (9%) had moderate disability (mRS score, 3). Most patients died (n=10) or experienced severe disability, defined as an mRS score of 4 or 5 (n=5). Asymptomatic intracerebral hemorrhage occurred in 3 patients (14%) and was nonfatal. Most patients aged 90 years or older who received intravenous tPA for acute ischemic stroke had poor 30-day functional outcomes or died. Intravenous tPA treatment in this age group does not improve the outcome of ischemic stroke.

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BI = Barthel Index; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; tPA = tissue plasminogen activator

People aged 85 years or older are the fastest growing segment of the older American population.¹ One in every 9 baby boomers will live to at least the age of 90 years,² and by 2050, it is estimated that there will be more than 55 million nonagenarians worldwide.³ Although age is a known risk factor for stroke, clinical trials have traditionally excluded⁴⁻⁹ or underrepresented¹⁰ patients older than 80

years. Intravenous tissue plasminogen activator (tPA) is the most beneficial therapy for emergent treatment of acute ischemic stroke.¹¹ Detailed outcomes of intravenous tPA administration in patients aged 90 years or older have not been published.

PATIENTS AND METHODS

We reviewed the medical records of patients aged 90 years or older who were treated with intravenous tPA for an acute ischemic stroke from March 1, 1999, to March 1, 2008. Patients were admitted to 1 of 3 Mayo Clinic sites (Rochester, MN; Scottsdale, AZ; or Jacksonville, FL) or the University of Alberta (Edmonton, AB). Databases including patients who received tPA were searched by date of birth. Patients were also identified through admission logs from the neurology and neurosurgery intensive care units. All patients given tPA were admitted to the intensive care unit for at least 24 hours after thrombolysis, according to the protocols followed at each institution. *International Classification of Diseases, Ninth Revision* coding for ischemic stroke was also used to search and confirm that all patients who had received tPA had been identified. Baseline functioning and comorbidities were determined by the clinical assessments on record before stroke presentation and the history provided at admission. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). Intravenous tPA protocol violations were identified using criteria from the National Institute of Neurological Disorders and Stroke (NINDS)⁴ study protocol and ECASS (European Cooperative Acute Stroke Study).⁵ Outcomes after intravenous tPA were quantitated by the Barthel Index (BI) and modified Rankin Scale (mRS) at 30- and 90-day follow-up. A favorable outcome was defined as an mRS score of 2 or less. Additional outcome measures after administration of intravenous tPA were the presence of intracerebral hemorrhage (ICH) and discharge site (nursing home, assisted living facility, or independent living facility). When death occurred, cause and circumstances were noted.

RESULTS

A total of 22 patients (11 women; median age, 93 years; range, 90-101 years) received intravenous tPA for symptoms

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FIGURE 1. Modified Rankin Scale (mRS) scores of patients aged 90 years or older before stroke (top bar) and 30 days after intravenous tissue plasminogen activator administration (bottom bar).

of acute ischemic stroke. Nearly all patients were highly functional at baseline (median mRS score, 1; BI, 95). Most patients (16 [73%]) performed their activities of daily living with little or no assistance before stroke. Comorbidities included hypertension (15 patients [68%]), atrial fibrillation (10 [45%]), symptomatic coronary artery disease (9 [41%]), congestive heart failure (6 [27%]), dyslipidemia (6 [27%]), Alzheimer dementia (1 [5%]), Lewy body dementia (1 [5%]), and mild cognitive impairment (1 [5%]).

The median NIHSS score on presentation was 16 (interquartile range, 11-19). More than half of the patients (14 [64%]) were severely affected at initial presentation (NIHSS score ≥ 15). The average time to treatment was 143 minutes (range, 90-180 minutes). All strokes were in the anterior circulation and deemed large vessel (17 [77%]), cardioembolic (3 [14%]), or indeterminate/cryptogenic (2 [9%]) in origin. There were no intravenous tPA protocol violations, and no differences in treatment protocols were identified among the 4 centers.

Asymptomatic ICH occurred in 3 patients (14%) and was detected incidentally on follow-up computed tomography of the head (2 patients) or magnetic resonance imaging of the brain (1 patient) within 36 hours of intravenous tPA administration.

After 30 days, 2 patients (9%) had a favorable outcome, 2 (9%) experienced moderate disability (mRS score, 3), 6 (27%) experienced severe disability (mRS score, 4-5), and 10 (45%) died (mean mRS score increase, 3.5; Figure 1). The mRS score at 30 days was unavailable

in 2 patients (9%), who were discharged from the hospital with an mRS score of 5. Although their mRS scores were unknown, both were alive 30 days after tPA administration. The median BI of surviving patients at 30-day follow-up was 20 (range, 0-90). All 6 patients with severe disability were discharged to a nursing home. The 2 patients with the highest prestroke mRS scores (mRS, 4) both died within 30 days. At 90 days, 9 patients (41%) were alive (Figure 2).

FIGURE 2. Survival of patients aged 90 years or older after administration of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke (n=22).

Poststroke survival in our cohort ranged from 4 days to 33 months. Information on the cause of death was available for all patients in the study. At the end of the study, 4 patients were alive, surviving 10, 24, 31, and 32 months after tPA administration.

Of the 14 patients (64%) with stroke evaluated using carotid artery ultrasonography, only 1 showed symptomatic stenosis. Of the 9 patients (41%) who underwent echocardiography (transesophageal, 6 [67%]; transthoracic: 3 [33%]), none experienced an intracardiac thrombus. Eight patients (36%) were in atrial fibrillation. Computed tomography of the head revealed evidence of infarction in all except one patient (21 [95%]). The 2 patients (9%) who underwent diffusion-weighted magnetic resonance imaging both had evidence of acute cerebral ischemia.

After tPA administration and hospitalization, 5 patients (23%) were given palliative care. For the 17 patients who died, the primary cause of death was the initial ischemic stroke (9 [53%]), aspiration pneumonia (3 [18%]), myocardial infarction (1 [6%]), or a second ischemic stroke more than 1 year later (1 [6%]). The cause of death was unknown or uncertain in 3 patients (17%), all of whom died after 90 days.

DISCUSSION

Good functional outcomes should not be expected when intravenous tPA is administered to nonagenarians with acute ischemic stroke. Our study cohort had higher 30- and 90-day mortality rates (55% and 59%, respectively) than those found in the available data for octogenarians^{11,12} and a similar mortality rate to that found in elderly patients with stroke who did not receive intravenous tPA.¹³ In contrast, a 90-day mortality rate of 32% to 40% is reported in the literature for intravenous tPA treatment of octogenarians after acute ischemic stroke.^{11,14}

Class I data are absent for tPA administration in the elderly population^{4,11-25} (Table). In the NINDS trial,²⁵ post hoc analysis of 49 patients older than 75 years found no support for subselection of patients for thrombolysis because of age. Nonetheless, tPA is not usually given to patients older than 80 years for reasons outside the traditional exclusion criteria.⁴ In some countries, intravenous tPA treatment is not recommended for elderly patients.

Previous studies have reported contradictory results on whether the rate of ICH is increased in carefully selected elderly patients. Notably, the high mortality rate in our study was not due to ICH, and tPA may be safer in this older age group than previously thought.

Withdrawal of support leading to respiratory failure was a major cause of death in our patients. Most of the patients who died did so as a direct result of the ischemic stroke. Treatment with tPA was not more likely than any other treatment to cause hemorrhage in the oldest old in our cohort. The rate of symptomatic ICH was reported to be 6.4% in the NINDS study,⁴ a cohort that included much younger patients. The lack of symptomatic ICH in our cohort may be due to the careful selection of patients aged 90 years or older for tPA administration.

Stroke severity is increased in the elderly population and is known to independently affect stroke outcomes.¹⁵ The patients in this study had more severe strokes (as defined by NIHSS scores) than those reported in other studies of younger cohorts, which suggests that the older group may a priori have worse outcomes with or without tPA.

This study has several limitations. First, it reports the results of a small cohort of elderly patients; however, currently it is the largest study of its kind. Other studies have included nonagenarians but have not focused on the oldest of the elderly patients. Second, because our analysis was retrospective, we were limited to the nonuniform decisions, investigations, and follow-up of clinicians at 4 different study centers. Finally, no comparison group was used. Age-matched patients with similar stroke severity who were not treated with thrombolytic agents were unavailable for comparison. Such a comparison would not have been ethical given the presumed benefits of tPA treatment in nonagenarians. Thus, our study did not allow us to arrive at conclusions about the efficacy of tPA treatment of stroke in nonagenarians. A randomized controlled trial of tPA treatment in elderly patients would be required.

The poor patient outcomes observed in this study were disconcerting because some recovery was expected and no intravenous tPA protocol violations occurred. Selection bias was likely because the final decision to administer tPA was made by the treating neurologist. However, the study patients presumably had the highest chance for improvement at the time of intravenous tPA administration.

CONCLUSION

Aggressive thrombolytic treatment with intravenous tPA is not futile in patients aged 90 years or older and is safe in carefully selected patients. However, functional outcomes are poor in most patients. In our study patients treated with intravenous tPA without protocol violations, 30-day survival was 55% and 90-day survival was 41%. Poor functional outcomes may also be related to the severity of the stroke on presentation.

TABLE. Summary of Research Articles on Acute Ischemic Stroke in Patients Aged 80 Years or Older^a

Reference	Study design	No. of patients ≥80 y	No. of patients receiving tPA	Age (y)	Major findings
NINDS Study Group, ⁴ 1995	Randomized controlled trial, 2 phases	42	42	UA	tPA, given within 3 h of symptomatic onset, improves clinical outcomes from ischemic stroke at 3 mo
NINDS Study Group, ²⁵ 1997	Post hoc analysis of patients >75 y	49 (>75 y)	49 (>75 y)	UA	No basis for subselection for treatment with tPA on the basis of age
Di Carlo et al, ¹⁶ 1999	Multicenter questionnaire and database comparison of patients <80 y and ≥80 y	1358	0	Mean, 85 Range, 80-102	Diagnostic tools such as brain imaging were used less often in patients ≥80 y; older patients had a worse prestroke mRS score; prestroke institutionalization strongly and independently predicted 3-mo disability in those ≥80 y
Sharma et al, ¹³ 1999	Prospective study comparing consecutive patients <75 y and ≥75 y	133 (≥75 y)	0 (≥75 y)	UA Maximum, 96	Older patients had a higher mortality and disability for the same severity of stroke vs younger patients; older age influenced 3-mo mortality; patients ≥75 y had more disabling strokes (by BI)
Tanne et al, ¹¹ 2000	Retrospective comparison of consecutive patients <80 y and ≥80 y from 13 US hospitals	30	30	Mean, 85 Range, 80-97	No evidence to withhold tPA on the basis of age in appropriately selected patients; similar rates of ICH in both age groups; higher in-hospital mortality and discharge to nursing home in patients ≥80 y; protocol violations reduced in patients ≥80 y
Heuschmann et al, ¹⁷ 2004	Pooled analysis of a large German stroke registry, comparing patients <75 y and ≥75 y	396 (≥75 y)	396 (≥75 y)	UA	Increasing age is associated with higher in-hospital mortality; rate of ICH after tPA increased with age (10.3% in patients ≥75 y)
Simon et al, ¹⁸ 2004	Comparison of patients <85 y and ≥85 y, based on prospective enrollment in a national Canadian database	62 (≥85 y)	62 (≥85 y)	Median, 84.0 Range, 80.1-94.8	Elderly patients have increased morbidity and mortality; treating these patients had a course similar to that of the natural history of stroke; patients should not be excluded from tPA because of their advanced age
Kammersgaard et al, ¹⁵ 2004	Follow-up data from stroke database in 7 European countries	191 (≥85 y)	0 (≥85 y)	Mean ± SD, 88±2.8	Age ≥85 y predicts short-term mortality or discharge to a nursing home; fewer older patients had hypertension and diabetes; more were female, lived alone, and had atrial fibrillation, preexisting disability, and a more severe stroke
Berrouschot et al, ¹⁹ 2005	Retrospective comparison of patients <80 y and ≥80 y at 3 German centers	38	38	Median, 83 Maximum, 91	No evidence to exclude older patients because of their age; older patients had a higher 90-d mortality and fewer achieved a favorable outcome (mRS ≤1); no increased risk of severe ICH in patients ≥80 y; no difference in onset to tPA treatment time or in NIHSS on presentation
Mouradian et al, ²⁰ 2005	Prospective study of patients who received tPA for 3 y, comparing those <80 y and ≥80 y	31	31	Range, 80-96	Older patients with more severe baseline NIHSS are less likely to benefit from tPA; 90-d mortality: 32% in older patients vs 11% in younger group; patients with NIHSS >11 and age >80 y were more than 10 times more likely to have poor outcome than those without these characteristics
Chen et al, ²¹ 2005	Retrospective study, comparing patients <80 y and ≥80 y	56	56	Mean, 84 Range, 80-93	Similar recanalization (by transcranial Doppler ultrasonography), 24-h improvement, and symptomatic ICH between groups; older patients had higher in-hospital mortality
Engelter et al, ²⁴ 2005	Retrospective study of multicenter tPA databank, comparing patients <80 y and ≥80 y	38	38	Mean, 84 Range, 80-92	Higher 3-mo mortality in older patients; age did not independently predict outcome; rates of sICH were similar between groups
Sylaja et al, ²³ 2006	Comparison of patients <80 y and ≥80 y, based on prospective enrollment in a national Canadian database	270	270	Mean ± SD, 84.7±3.6	sICH rate not increased in carefully selected elderly patients; favorable outcome (mRS 0-1) more likely in 26% of older patients vs 40% of younger patients
van Oostenbrugge et al, ¹⁴ 2006	Retrospective comparison of patients <80 y and ≥80 y	45	45	Mean, 85 Median, 84 Range, 80-97	Good outcome (mRS ≤2) in 36% of patients ≥80 y and 63% of those <80 y; sICH found in 11.1% of patients ≥80 y and 2.9% of those <80 y
Engelter et al, ²² 2006	Review of 6 other studies	477	477	UA	Older patients are less likely to receive tPA under protocol violations; 3 times higher 3-mo mortality in patients ≥80 y with less likelihood of gaining a favorable outcome (mRS ≤1); similar likelihood of sICH in both age groups
Zeevi et al, ¹² 2007	Retrospective comparison of patients <80 y and ≥80 y	341	UA (some)	UA	tPA is safe and efficacious in older patients; no excess risk of sICH in the older age group; older patients were less likely to be treated with tPA even when lacking traditional exclusion criteria

^a BI = Barthel Index; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; sICH = symptomatic intracerebral hemorrhage; tPA = tissue plasminogen activator; UA = unavailable.

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