Impact of Acute Ischemic Stroke Treatment in Patients >80 Years of Age

The Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) Consortium Experience

Joshua Z. Willey, MD, MSC*; Santiago Ortega-Gutierrez, MD, MSc*; Nils Petersen, MD; Pooja Khatri, MD; Andria L. Ford, MD; Natalia S. Rost, MD; Latisha K. Ali, MD; Nichole R. Gonzales, MD; Jose G. Merino, MD; Brett C. Meyer, MD; Randolph S. Marshall, MD, MS

Background and Purpose—Few studies have addressed outcomes among patients ≥80 years treated with acute stroke therapy. In this study, we outline in-hospital outcomes in (1) patients ≥80 years compared with their younger counterparts; and (2) those over >80 years receiving intra-arterial therapy (IAT) compared with those treated with intravenous recombinant tissue-type plasminogen activator (IV rtPA).

Methods—Stroke centers within the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) prospectively collected data on all patients treated with IV rtPA or IAT from January 1, 2005, to December 31, 2010. IAT was defined as receiving any endovascular therapy; IAT was further divided into bridging therapy when the patient received both IAT and IV rtPA and endovascular therapy alone. In-hospital mortality was compared in (1) all patients aged ≥80 years versus younger counterparts; and (2) IAT, bridging therapy, and endovascular therapy alone versus IV rtPA only among those age ≥80 years using multivariable logistic regression. An age-stratified analysis was also performed.

Results—A total of 3768 patients were included in the study; 3378 were treated with IV rtPA alone and 808 with IAT (383 with endovascular therapy alone and 425 with bridging therapy). Patients ≥80 years (n=1182) had a higher risk of in-hospital mortality compared with younger counterparts regardless of treatment modality (OR, 2.13; 95% CI, 1.60–2.84). When limited to those aged ≥80 years, IAT (OR, 0.95; 95% CI, 0.60–1.49), bridging therapy (OR, 0.82; 95% CI, 0.47–1.45), or endovascular therapy alone (OR, 1.15; 95% CI, 0.64–2.08) versus IV rtPA were not associated with increased in-hospital mortality.

Conclusions—IAT does not appear to increase the risk of in-hospital mortality among those aged ≥80 years compared with IV thrombolysis alone. (Stroke. 2012;43:00-00.)

Key Words: acute Rx ■ acute stroke ■ interventional neuroradiology

The incidence of ischemic stroke increases with age and is particularly high in people aged >80 years.1 Compared with younger patients, ischemic stroke is more likely to be associated with severe neurological impairment, larger infarct volume, and higher morbidity and mortality rates in older patients.1 In-hospital complications including stroke expansion, hemorrhagic transformation, pneumonia, urinary tract infections, cardiac complications, and mortality are more likely in patients aged ≥80 years compared with younger patients.2,3 Perhaps because of the greater impairment and disability in this age group, treatment with intravenous recombinant tissue-type plasminogen activator (IV rtPA) remains controversial for some practitioners2 and has not been approved by the European Medicines Evaluations Agency.3 Clinical trials in acute stroke have previously excluded octogenarians.4 5 Controversy over how to treat older patients mainly stems from concern over excess risk of hemorrhage, lower likelihood of clinical benefit,6–12 and...
higher in-hospital and 3-month mortality. However, despite increased complications, this patient population still appears to benefit from thrombolysis, although in the National Institute of Neurological Disorders and Stroke tPA trial, only a small proportion of participants were age >80 years.

With the emergence of endovascular therapy, there has been an increased interest in determining whether this treatment modality is safe in older patients. Endovascular treatment has been associated with higher mortality rates and lower likelihood of clinical benefit among patients aged >80 years, although some older patients may still benefit from endovascular therapy. In the present study, we aimed to evaluate mortality and hospital disposition outcomes in patients ≥80 years treated with endovascular therapy. We hypothesized that because of higher complication rates overall in this population, (1) treatment with endovascular therapy would be associated with a greater risk of in-hospital mortality in patients ≥80 years compared to younger counterparts; but (2) in-hospital mortality would be similar among those ≥80 years receiving endovascular therapy versus IV rtPA.

Methods

Patient Selection and Data Collection

This is a retrospective analysis of prospectively collected patients with acute stroke admitted to Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) centers between January 1, 2005, and December 31, 2010. The study was approved by the Institutional Review Board at each center.

SPOTRIAS is a National Institutes of Health-funded program consisting of 8 academic stroke programs with the central aim of testing novel stroke treatments in the Phase I and II stages (see “Acknowledgments”). Each SPOTRIAS center maintains a prospective acute stroke patient database that collects admission and in-hospital characteristics as well as clinical outcomes in all patients who either received acute stroke treatments or are enrolled in one of the SPOTRIAS clinical trials. We examined data from all patients from the SPOTRIAS database who received acute stroke therapy. Demographic and clinical data elements collected for the SPOTRIAS consortium database included age, race–ethnicity, sex, pretreatment National Institutes of Health Stroke Scale (NIHSS), acute stroke treatment modality, discharge destination, and in-hospital mortality.

Pre-stroke modified Rankin Scale was collected at only 6 sites (n=2074). Ninety-day clinical outcomes, information regarding symptomatic intracranial hemorrhage, modified Rankin Scale, and causes of death were available in only a limited number of patients; time to treatment with IV rtPA and intra-arterial therapy was not captured.

Data and Statistical Analysis

For our first hypothesis the principal explanatory variable was being aged ≥80 years. For our second hypothesis the principal explanatory variable was intra-arterial therapy (IAT), defined as receiving any intra-arterial pharmacological or mechanical endovascular treatment regardless of preceding IV rtPA. IAT was further divided into bridging therapy (BT) when the patient received both IAT and IV rtPA and endovascular therapy alone (ETA) when patients did not receive IV rtPA before endovascular treatment. Outcome measures were in-hospital mortality and discharge to a facility other than home.

Continuous variables were first dichotomized to relevant clinical cut points. Patients were divided into 2 age categories (<80 and ≥80 years) based on common exclusion criteria of several recent clinical trials such as Pro-Urokinase for Acute Cerebral Thromboembolism (PROACT-II), Interventional Management of Stroke (IMS) III, and European Cooperative Acute Stroke Study (ECASS) III and the ongoing clinical concern about treating octogenarians with IAT. To evaluate the influence of age on mortality for each treatment group, an age-stratified analysis was performed. Age was stratified in decades; age <50 years selected as the reference category. Severe stroke was defined as NIHSS ≥12. Initial proportions for each treatment arm were calculated for descriptive statistics. Categorical variables were assessed in a univariate analysis using χ² analysis. Multivariable logistic regression was used to assess for independent associations between age and IAT with in-hospital mortality and discharge disposition. We first performed univariate analyses (Model 1) followed by a model adjusted for baseline demographics: sex, race–ethnicity, and SPOTRIAS center (Model 2). Our final model (Model 3) was further adjusted for our hypothesized principal confounders: NIHSS and serum glucose level. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC); P≤0.05 was set as statistically significant.

Results

Baseline Characteristics

A total of 3768 patients were treated with acute stroke therapy across the SPOTRIAS consortium over 6 years; 3378 were treated with IV rtPA alone and 808 with IAT (383 with ETA and 425 with BT). Baseline demographics were similar between the different treatment groups as outlined in Table 1. Patients were predominantly white non-Hispanic with approximately 50% males. The proportion of all patients treated with IV rtPA who were ≥80 years was 34.2% and varied significantly between the centers (19.4%–50.4%, P<0.0001). In comparison, 23% of patients in the IAT group were ≥80 years (21.9% in ETA group and 24% in BT group; Table 1). Octogenarians were more likely to have severe strokes (NIHSS ≥12; 64.9% versus 48.4%, P<0.0001) and were less likely to receive BT (9.5% versus 14.5%, P<0.0001) when compared with younger patients. When limited to those patients with an NIHSS ≥12, patients ≥80 years were less likely to receive IAT (12.8% versus 24.6%, P<0.0001). Overall, a total of 431 (12.1%) deaths were reported and 2412 (64.0%) patients were not discharged home.

In-Hospital Outcomes in Patients Aged >80 Years Compared With Younger Patients

Patients ≥80 years treated with IV rtPA alone had a higher risk of in-hospital mortality (Model 3: adjusted OR, 2.13; 95% CI, 1.60–2.84) and of having a disposition other than home (Model 3: adjusted OR, 2.51; 95% CI, 2.03–3.11) compared with younger patients. Octogenarians who were treated with IAT also demonstrated increased mortality compared with younger counterparts (Model 3: adjusted OR, 1.98; 95% CI, 1.29–3.04). Similar results were noted in patients ≥80 years versus younger counterparts for ETA (Model 3: adjusted OR, 2.44; 95% CI, 1.30–4.59) but not BT (Model 3: adjusted OR, 1.65; 95% CI, 0.91–2.98). A higher risk of not being discharged home was noted for all treatment modalities except for ETA (Model 3: adjusted OR, 1.55; 95% CI, 0.68–3.55). In addition, the association of disposition other than home with BT was disproportionally higher (Model 3: OR, 9.41; 95% CI, 2.64–33.6) when compared with the other treatment modalities (online-only Data Supplement Table I).
Age Influence on In-Hospital Outcomes

Univariate and multivariable analysis categorizing age as deciles revealed that the likelihood of mortality increased with age regardless of the treatment. Additionally, the rate of rise in ORs was more notable at the 80- to 89-year strata in unadjusted and adjusted models (Figure 1). When IV rtPA was used, the odds of in-hospital mortality in the 80- to 89-year age strata increased 1.48 times when compared with the 70- to 79-year category after adjusting for sex, race–ethnicity, SPOTRIAS center, NIHSS, and glucose serum levels (from OR, 2.53; 95% CI, 1.36–4.72 to OR, 3.75; 95% CI, 2.03–6.94). Similarly, the adjusted odds of mortality increased 1.54 times when the 80- to 89-year group was compared with the 80- to 89-year strata (OR, 3.88; 95% CI, 1.68–8.98 to OR, 6.18; 95% CI, 2.57–14.83). A similar pattern of increase was encountered when discharge disposition was used as the outcome (Figure 2).

In-Hospital Outcomes Among Octogenarians Comparing Endovascular Therapy With IV rtPA

The univariate analyses showed that all endovascular therapies were associated with an increased risk of in-hospital mortality when compared with IV rtPA (Table 2). However, in adjusted models, all of the associations were no longer significant (Model 3: IAT versus IV rtPA adjusted OR, 0.95; 95% CI, 0.60–1.49; Model 3: BT versus IV rtPA adjusted OR, 0.82; 95% CI, 0.47–1.45; Model 3: ETA versus IV rtPA adjusted OR, 1.15; 95% CI, 0.64–2.08).

Given the importance of NIHSS on the decision to proceed with IAT, we carried out further analyses only among those aged ≥80 years with an NIHSS ≥12 (n=751) and found no evidence for increased mortality. In our final models (Model 3), IAT (adjusted OR, 0.79; 95% CI, 0.49–1.29), BT (adjusted OR, 0.79; 95% CI, 0.44–1.42), and ETA (adjusted OR, 0.92; 95% CI, 0.48–1.77) versus IV rtPA were not associated with increased mortality.

Because only 68 patients with age ≥80 years and an NIHSS ≥12 (9.1%) were discharged home, no analysis comparing the different treatment modalities was performed on this subgroup alone.

Outcomes Among Those Restricted to Arrival Within 3 Hours of Stroke Onset

An additional analysis was performed restricted to those patients who arrived <3 hours and received IV rtPA alone versus endovascular therapy alone regardless of patient age. A total of 94 patients who arrived within 3 hours received ETA. Reported exclusion reasons for IV rtPA included: age ≥80 (18), international normalized ratio ≥1.7 (8), abnormal platelet count (8), could not be treated within 3 hours (8), intracerebral hemorrhage history (2), elevated NIHSS (one), and no other reason listed (49). Univariate analysis revealed that ETA was associated with a greater risk of in-hospital mortality when compared with IV rtPA (OR, 3.80; 95% CI, 2.20–6.54). These results persisted after adjusting for sex, race–ethnicity, center, and NIHSS, suggesting that ETA was associated with a greater risk of in-hospital mortality (OR, 3.97; 95% CI, 2.00–7.87). Interestingly, results were similar when restricted to patients who were over aged >80 years (n=18; adjusted OR, 5.52; 95% CI, 1.24–25.0).

Discussion

This is the largest study of endovascular therapy in patients ≥80 years of age. The results of our study suggest that: (1) in-hospital outcome measured by mortality and disposition were worse in those aged ≥80 years compared with their younger counterparts; and (2) acute endovascular treatment of stroke using IAT, ETA, or BT was not associated with an
increase mortality in those aged ≥80 years when compared with IV rtPA, including among those with severe strokes. In secondary analyses we also found that (1) aging is associated with mortality and being discharged other than home regardless of the treatment used; and (2) the use of endovascular therapy <3 hours without IV rtPA was associated with an increased mortality compared IV rtPA alone.

Data from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) registry evaluated >1000 patients aged ≥80 years who received IV rtPA and compared outcomes with younger patients. In keeping with our results, the authors reported a higher mortality and a worse 3-month functional outcomes in older versus younger patients. These findings are consistent with the overall worse prognosis in this age group regardless of treatment offered.28 Part of this effect may be due to the presence of a higher prestroke functional disability, more medical comorbidities,29,30 or a baseline risk of neurological complications such as infarct expansion. Nonetheless, an independent effect of age on outcomes is noted in these studies and could reflect further unmeasured confounders, a particular susceptibility to ischemic brain injury, or poor development of collaterals.31 The risks for hemorrhagic conversion and symptomatic intracranial hemorrhage, on the other hand, do not appear to be higher among octogenarians.32,33 Several case series have documented a lower probability of a good neurological outcome at discharge or at 90 days using endovascular therapy among those aged ≥80 years compared with their younger counterparts.16,24,25 In our study, however, we showed that in-hospital mortality associated with endovascular therapies was not different in patients aged ≥80 years using control subjects of the same age group and after adjustment for pretreatment NIHSS.

Our results are also unique in comparing IV rtPA treatment with a small sample of patients who were treated with ETA despite arriving within 3 hours of stroke onset. We noted in this group that ETA led to poorer outcomes despite having adjusted for stroke severity. The principal reasons for exclusion from IV rtPA were age and coagulopathy. Interestingly, results remained the same when the comparison was performed among patients aged ≥80 years, stressing the point IV rtPA remains gold standard for acute stroke treatment. Although there may be unmeasured confounders that could contribute to the difference in outcome, our results caution against proceeding with ETA without first administering IV rtPA to eligible patients.

Our study has several weaknesses that should be considered. First, no information regarding time from stroke onset
to treatment, multimodal imaging, or recanalization was collected. Faster treatment may have resulted in better recanalization, and those with proximal occlusions and larger penumbra based on multimodal imaging may have been more likely to be treated with endovascular therapy, leading to a bias toward better outcomes in this group. Second, we did not systematically collect data on symptomatic intracerebral hemorrhage, procedural complications, or detailed premorbid

Figure 2. A–D, Age effect on discharge disposition other than home in different acute stroke therapies. IV rtPA indicates intravenous recombinant tissue-type plasminogen activator alone; IAT, any intra-arterial therapy; ETA, endovascular therapy alone; Ref, reference category; Unadjusted, univariate analysis; Adjusted, multivariable analysis adjusted for sex, race–ethnicity, and Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) center, National Institutes of Health Stroke Scale, and serum glucose level.

Table 2. In-Hospital Mortality Among Patients With Acute Ischemic Stroke Aged >80 Y Based on Treatment Modality

<table>
<thead>
<tr>
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<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
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<tr>
<td>All patients with acute ischemic stroke</td>
<td></td>
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<tr>
<td>IAT versus IV rtPA</td>
<td>1.93 1.34–2.79</td>
<td>1.46 0.97–2.20</td>
<td>0.95 0.60–1.49</td>
</tr>
<tr>
<td>BT versus IV rtPA</td>
<td>1.72 1.07–2.77</td>
<td>1.34 0.80–2.24</td>
<td>0.82 0.47–1.45</td>
</tr>
<tr>
<td>ETA versus IV rtPA</td>
<td>2.08 1.27–3.43</td>
<td>1.53 0.89–2.63</td>
<td>1.15 0.64–2.08</td>
</tr>
<tr>
<td>All patients in whom NIHSS &gt;12</td>
<td></td>
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<tr>
<td>IAT versus IV rtPA</td>
<td>1.32 0.88–1.98</td>
<td>0.96 0.61–1.52</td>
<td>0.79 0.49–1.29</td>
</tr>
<tr>
<td>BT versus IV rtPA</td>
<td>1.21 0.73–2.02</td>
<td>0.92 0.53–1.59</td>
<td>0.79 0.44–1.42</td>
</tr>
<tr>
<td>ETA versus IV rtPA</td>
<td>1.45 0.82–2.57</td>
<td>1.09 0.58–2.04</td>
<td>0.92 0.48–1.77</td>
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Model 1: univariate analysis; Model 2, Model 1 further adjusted for sex, race–ethnicity, and Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) center; Model 3, Model 2 further adjusted for National Institutes of Health Stroke Scale and serum glucose level.

IAT indicates any intra-arterial therapy; IV rtPA, intravenous recombinant tissue-type plasminogen activator alone; BT, bridging therapy; ETA, endovascular therapy alone; NIHSS, National Institutes of Health Stroke Scale.
functional status. Symptomatic intracerebral hemorrhage is associated with significant morbidity and mortality that could have skewed our results against endovascular therapy; on the other hand, we did not find an increased risk of death. In addition, data on premorbid functional status were only collected at 6 sites and overall in less than half of all patients. We did not have additional information on medical comorbidities, premorbid frailty, or dementia, which are likely to contribute to poststroke outcomes and treatment selection bias. Lastly, we did not collect 90-day outcomes such as the modified Rankin Scale, which is considered a standard outcome for stroke studies. However, given that our focus was on identifying negative outcomes related to each treatment modality, these are unlikely to change dramatically after hospital discharge because improvement is expected after stroke.

Our findings suggest that endovascular therapy among patients >80 years does not increase in-hospital mortality when compared with patients of the same age receiving only IV rtPA. Advance age increases the likelihood of poor outcome regardless of the treatment, however, particularly in the transition from the seventh to the eighth decade. In addition, we found increased mortality among patients who received endovascular treatment <3 hours when IV rtPA was contraindicated, suggesting that endovascular treatment might not benefit everyone. Whether older patients should ultimately be treated with endovascular therapy with or without IV rtPA can only be answered through a clinical trial. These trials should recruit participants aged >80 years and include clinical variables that may influence outcomes in this age group including frailty and cognition measures and a comprehensive assessment of comorbidities. In the interim our data would suggest that these patients can be safely enrolled. The routine clinical use of IAT, especially in this age group, however, remains as of yet experimental.

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Disclosures

None.

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