Published in final edited form as:

Neurologist. 2012 March ; 18(2): 99–101. doi:10.1097/NRL.0b013e318248ea3c.

Safety of thrombolysis in patients over the age of 80

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Abstract

Background—The safety of intravenous thrombolysis (IVT) in patients with acute ischemic stroke over age 80 is unclear. We hypothesized that patients over age 80 can be safely treated with IVT.

Methods—Admission and discharge data were collected on all patients at a single tertiary care center presenting within 12 hours of onset. Collected data included treatment with IVT, demographics, pre-treatment National Institutes of Health Stroke Scale (NIHSS) score, length of stay (LOS), mortality and discharge disposition. Analyses were restricted to patients over age 80, and the primary outcome was in-hospital mortality. Logistic regression was used to examine whether IVT was associated with mortality.

Results—Between 1/1/05 and 6/30/10, 112 patients over age 80 presented within 3 hours of ischemic stroke onset, and 31 received IVT. There were 15 deaths. In multi-variable models adjusted for age, sex, race-ethnicity and NIHSS, treatment with IVT compared to no treatment, was not associated with in-hospital death (adjusted OR 1.2, 95% confidence interval 0.3 – 4.3).

Conclusions—Treating ischemic stroke patients over 80 with IVT was not associated with an increase in mortality in an urban tertiary care center.

Introduction

The only approved treatment for acute ischemic stroke is intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator¹. When administered within 4.5 hours from ischemic stroke onset IVT improves functional outcomes at 3 months, is cost-effective, and has an excellent safety profile^{1,2}. A common exclusion criterion for IVT under 3 hours from onset is age over 80³, though the NINDS t-PA trial did not include an age limit for inclusion and no age cut-off is mentioned in American Heart Association guidelines for patients treated under 3 hours from onset¹. On the other hand IVT is not recommended for patients presenting between 3 to 4 ½ hours who are over age 80 since they were excluded from the European Cooperative Acute Stroke Study III². Several investigators have raised the concern that those over age 80 may derive less clinical benefit from IVT, or that their rate of hemorrhage is higher than in younger patients^{4–7}. In this study we compared in-hospital mortality in patients over age 80 who arrived within 3 hours from onset by whether they received IVT; secondary outcomes included length of stay (LOS), symptomatic hemorrhage, and discharge disposition.

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The authors report no financial conflicts of interest

Methods

Our data were drawn from the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) program at Columbia University Medical Center. We collected data on all patients who presented to the emergency room within 12 hours from stroke onset and who either consented to participate in a registry or trial, or were included by means of an institutional review board (IRB)-approved waiver of consent. Our analysis was limited to those admitted between 12/1/2004 and 6/30/2010. We analyzed discharge outcomes for patients over age 80 who arrived into the emergency room within 3 hours of ischemic stroke onset. Clinical information obtained in all patients included socio-demographic variables (age, sex, and race-ethnicity), initial NIHSS, treatment with IVT, discharge disposition, LOS, mortality, and 24 hour neuro-imaging (magnetic resonance imaging or computer tomography). A CT head and NIHSS is performed on all patients 24 hours after IVT. Pre-admission functional status was not available in a large proportion of patients. Symptomatic intracranial hemorrhage (sICH) was defined as any hemorrhage on neuro-imaging with an associated increase in the NIHSS of $\geq 4^8$.

The primary exposure of interest was IVT and our primary outcome measure was in-hospital mortality. Secondary outcomes of interest included discharge disposition (defined as discharge to home versus all others), hospital LOS, and sICH.

Baseline demographics of those who were treated versus not treated with IVT were compared using a 2 sided t-test for continuous variables, and a chi-squared test for categorical variables. Contingency tables and multi-variable logistic regression was used to derive odds ratios (OR) and 95% confidence intervals (CI) for mortality and discharge disposition based on IVT; models were adjusted for age, sex, race-ethnicity, and pre-treatment NIHSS. We did not adjust for further variables given the small sample size to avoid over-adjusting our models. In order to examine whether IVT influenced LOS, linear regression models were calculated in a similar manner. All analyses were carried out with SAS version 9.2 (Cary, NC).

Results

The baseline demographics of the sample are presented in table 1. A total of 112 patients over age 80 presented within 3 hours of ischemic stroke onset (age range 80–101), and 31 received IVT. The principal reasons for not administering IVT were rapidly improving deficit (n=37) and/or the inability to initiate treatment within 3 hours (n=30). The median NIHSS score in all patients was 6 (inter-quartile range (IQR) 1–16), and was lower in those patients who were untreated (median 4, IQR 1–11) versus treated (median 14, IQR 8–22). There were no other differences in baseline demographics.

There were 15 in-hospital deaths among all patients, and 60 were not discharged home. In multi-variable analyses IVT (versus no treatment) was not associated with an increased risk of in-hospital death (adjusted OR 1.2, 95%CI 0.3–4.3), and was associated with a trend towards disposition other than to home (adjusted OR 2.9, 95%CI 0.9–8.9). The mean LOS was 6.7 days, and was 3.4 days longer in those treated with IVT. There was one symptomatic hemorrhage (3%) in the IVT treated group.

Discussion

In this sample of patients over the age of 80 who arrived to the emergency room within three hours, those who were treated with IVT did not have an increased risk of death compared to those not treated, and had an acceptably low hemorrhage rate. Our results add to the indirect evidence of the safety of IVT in patients over the age of 80, which in combination with

clinical trial data, indicate that age should not be an exclusion criterion from treatment. Our findings are notable given that removal of an exclusion criterion of age 80 could increase the proportion of IVT treated patients by close to 10%⁹. In our study, patients treated with IVT had more severe strokes, which was reflected in the longer LOS and a trend towards not being discharged home, and yet this did not translate to a higher risk of sICH or death. The reports regarding safety of IVT in octogenarians were likely driven by stroke severity and pre-stroke functional status^{5,10}, as well as by selection of controls who were younger than age 80. Older patients are more likely to have severe strokes due to the high prevalence of atrial fibrillation and poor outcomes appear to be driven by in-hospital medical complications that could also affect length of stay^{11–13}. A more severe deficit would also make it less likely for a patient to be discharged home.

Our institution does not have formal criteria for excluding patients from IVT based on age, though clinicians in this age group may look for other reasons not to treat. In keeping with this hypothesis we found it noteworthy that a high proportion of participants over the age of 80 were not treated due to a mild or rapidly improving deficit. Others have noted that those over 80 are less likely to have protocol violations when given IVT¹⁴. Our results differ from others who report that treatment in those over 80 is associated with poor outcomes^{4,5,11,15–17}, and could be related to our control group were other patients presenting under 3 hours who were also over age 80 and therefore likely to have a poor outcome regardless of IVT.

Our study however has some important limitations. Our sample size was small, and therefore we cannot exclude the possibility that we were underpowered to detect a difference in mortality rates. We did not collect information on in-hospital complications, including pneumonia and other infections, or other markers of pre-stroke comorbidity. There is likely to be residual confounding related to stroke severity that we were not able to adjust for in our models. It is likely that pre-hospital functional status and stroke severity interact with age to influence outcome after IVT¹¹. We did not carry out an efficacy study, which should include 90 day outcomes and a random assignment to IVT, and we can therefore not comment on long term clinical efficacy in this age group. Nonetheless previous analyses have shown that those over 80 may benefit from treatment with IVT^{18,19}. A review of the Safe Implementation of Treatment in Stroke – International Stroke Thrombolysis Registry (SITS-ISTR) and Virtual International Stroke Trials Archive (VISTA) showed that age was a significant predictor of poor outcome, but that nonetheless older patients continued to receive a benefit from thrombolysis²⁰. In order to show a more robust clinical benefit in those over age 80 registries and clinical trials will need to consider pre-morbid functional status, stroke severity, and meaningful clinical outcomes. Our analyses support that these patients can have an excellent safety profile and therefore age over 80 should not be considered a contraindication for IVT.

Acknowledgments

This study was funded by the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) initiative at Columbia University Medical Center, NINDS P50 NS049060. Jzw was funded by NINDS 1K23NS073104-01A1

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Baseline demographics of patients over the age of 80 and arriving to the emergency room within 3 hours from ischemic stroke onset

Table 1

	All participants (n=112). Mean (+/- standard deviation), or number (proportion)	Treated with IV rtPA (n = 31). Mean (+/- standard deviation), or number (proportion)	Not treated with IV rtPA (n= 81). Mean (+/- standard deviation), or number (proportion)	p-value for difference
Age	86.2(4.6)	87.5(4.7)	85.8(4.5)	0.7
Women	86(76.8%)	25(80.6%)	61(75.3%)	0.5
Race-ethnicity				0.8
Hispanic	48(43.6%)	13(41.9%)	35(43.2%)	
Black	20(18.2%)	5(16.1%)	15(18.5%)	
White	44(38.2%)	13(42.0%)	31(48.3%)	
Deaths	15(13.4%)	7(22.6%)	8(9.9%)	0.07
Discharge other than to home	52(46.4%)	24(77.4%)	28(34.6%)	<0.0001
Median NIHSS (Inter-quartile range)	6(1-16)	14(8-22)	4(1-11)	<0.0001
Length of stay in days	6.7(6.9)	9.4(9.2)	5.7(5.6)	0.04

Table 2

In-hospital outcomes in patients over the age of 80 who were treated with intravenous recombinant tissue plasminogen activator compared to those who were not treated (reference).

	Univariate (Odds ratio, 95% confidence interval; or parameter estimate for linear regression) [‡]	Multi-variable analysis (Odds ratio, 95% confidence interval; or parameter estimate for linear regression) ^{*‡}
Death	2.7(0.9–8.1)	1.2(0.3–4.3)
Discharge other than to home	6.5(2.5–16)	2.9(0.9–8.9)
Length of stay difference (p-value)	3.7(0.04)	3.4(0.04)

* adjusted for age, sex, race-ethnicity, and pre-treatment NIHSS

[‡] Odds ratios represent odds of the outcomes among those treated versus those who were not treated.