Published in final edited form as:

J Stroke Cerebrovasc Dis. 2014 July ; 23(6): 1657–1661. doi:10.1016/j.jstrokecerebrovasdis.2014.01.011.

Safety of Intravenous Tissue Plasminogen Activator Administration with Computed Tomography Evidence of Prior Infarction

Michael J. Lyerly, MD^{*,†,1}, J. Thomas Houston, MD^{*,1}, Amelia K. Boehme, MSPH^{*,‡}, Karen C. Albright, DO, MPH^{‡,§,||}, Reza Bavarsad Shahripour, MD^{*}, Paola Palazzo, MD^{*}, Muhammed Alvi, MD^{*}, Pawan V. Rawal, MD^{*}, Niren Kapoor, MD^{*}, April Sisson, RN^{*}, Anne W. Alexandrov, PhD^{*,¶}, and Andrei V. Alexandrov, MD^{*}

^{*}Stroke Center, Department of Neurology, University of Alabama at Birmingham

[†]Birmingham Veterans Administration Medical Center, Birmingham, Alabama

[‡]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama

[§]Health Services and Outcomes Research Center for Outcome and Effectiveness Research and Education (COERE), Birmingham, Alabama

^{||}Center of Excellence in Comparative Effectiveness Research for Eliminating Disparities (CERED), Minority Health & Health Disparities Research Center (MHRC), Birmingham, Alabama

[¶]School of Nursing, University of Alabama at Birmingham, Birmingham, Alabama

Abstract

Background—Prior stroke within 3 months excludes patients from thrombolysis; however, patients may have computed tomography (CT) evidence of prior infarct, often of unknown time of origin. We aimed to determine if the presence of a previous infarct on pretreatment CT is a predictor of hemorrhagic complications and functional outcomes after the administration of intravenous (IV) tissue plasminogen activator (tPA).

Methods—We retrospectively analyzed consecutive patients treated with IV tPA at our institution from 2009–2011. Pretreatment CTs were reviewed for evidence of any prior infarct. Further review determined if any hemorrhagic transformation (HT) or symptomatic intracerebral hemorrhage (sICH) were present on repeat CT or magnetic resonance imaging. Outcomes included sICH, any HT, poor functional outcome (modified Rankin Scale score of 4–6), and discharge disposition.

Results—Of 212 IV tPA-treated patients, 84 (40%) had evidence of prior infarct on pretreatment CT. Patients with prior infarcts on CT were older (median age, 72 versus 65 years; $P = .001$) and

Address correspondence to Michael J. Lyerly, MD, Stroke Program, Department of Neurology, RWUH 226, 1720 2nd Avenue S, Birmingham, AL 35294-0001. mjlyerly@uab.edu.

¹The authors contributed equally to this work.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality, the American Heart Association, or the National Institutes of Health.

had higher pretreatment National Institutes of Health Stroke Scale scores (median, 10 versus 7; $P = .023$). Patients with prior infarcts on CT did not experience more sICH (4% versus 2%; $P = .221$) or any HT (18% versus 14%; $P = .471$). These patients did have a higher frequency of poor functional outcome at discharge (82% versus 50%; $P < .001$) and were less often discharged to home or inpatient rehabilitation center (61% versus 73%; $P = .065$).

Conclusions—Visualization of prior infarcts on pretreatment CT did not predict an increased risk of sICH in our study and should not be viewed as a reason to withhold systemic tPA treatment after clinically evident strokes within 3 months were excluded.

Keywords

Acute ischemic stroke; thrombolysis; safety; symptomatic intracerebral hemorrhage; computerized tomography

Introduction

Systemic thrombolytic therapy has been shown to improve clinical outcomes in patients with acute ischemic stroke.¹ The most feared adverse effect of intravenous (IV) tissue plasminogen activator (tPA) is symptomatic intracerebral hemorrhage (sICH) because of the high associated morbidity and mortality.² Generally, tPA protocols derived from the original National Institute of Neurological Disorders and Stroke tPA trial¹ aim to exclude patients who are considered to be at high risk for sICH. One of these exclusions is a history of stroke within the preceding 3 months. Unfortunately, patients may not be able to report this history and physicians may have to use their best judgment when the pretreatment CT scan reveals evidence of prior infarction.

Pretreatment magnetic resonance imaging (MRI) studies have shown that absolute volume on diffusion weighted imaging^{3,4} and fluid attenuated inversion recovery hyperintensities within the area of diffusion restriction are associated with increased risk of hemorrhagic transformation (HT) after IV thrombolysis.⁵ However, given the current lack of adequate MRI availability and the extended study duration compared with CT, the application of these findings is of limited value in clinical practice. Several indicators on the pretreatment CT scan have been identified as risk factors for sICH, including early ischemic changes and a hyperdense middle cerebral artery sign.^{6,7} Unfortunately, changes associated with previous infarcts have not been well studied to determine their risk of sICH. The purpose of this study was to determine if there is a relationship between evidence of prior infarction on pretreatment CT, either lacunar or cortical, and subsequent sICH in patients receiving IV tPA.

Methods

Study Population and Variable Definition

We retrospectively identified all consecutive IV tPA-treated patients who presented to our tertiary care center from 2008–2011 using our prospectively collected stroke registry. Patients were excluded if they were transferred from another institution. Patient demographic, clinical, and imaging data were extracted from the medical record. Stroke

severity was measured using the National Institutes of Health Stroke Scale (NIHSS) score. Pretreatment CTs were reviewed for evidence of any prior infarct by neurologists blinded to follow-up imaging. The definition of a prior infarct was at the clinical discretion of the neurologist and confirmed by an independent review by a neuroradiologist. We did not distinguish these prior infarctions as symptomatic or asymptomatic. Patients with evidence of prior infarct were subdivided into prior lacunar or prior cortical infarcts. These groups were not mutually exclusive as patients could have evidence of both prior lacunar and cortical infarcts. After all pretreatment head CTs were reviewed, repeat CT or MRI was evaluated to determine if hemorrhage was present.

Outcomes of interest included any HT on follow-up CT or MRI, sICH (defined as a type 2 parenchymal hemorrhage with deterioration in the NIHSS score of ≥ 4 points or death⁸), poor functional outcome (defined as a modified Rankin Scale score of 3–6), and favorable discharge disposition (being discharged to home or an inpatient rehabilitation center). We compared admission, clinical, and discharge information between patients who had evidence of prior infarct compared with those who did not have prior evidence of infarct.

Statistics

Demographic and clinical data were recorded throughout admission and compared between groups using chi-square and *t* tests with nonparametric equivalents when appropriate. Crude and adjusted logistic regression analyses were conducted to assess the relationship between evidence of prior infarct and outcomes of interest. Adjustment variables for the multivariable logistic regression models were chosen based on baseline differences between the 2 groups and clinical significance. As this was an exploratory analysis, no adjustments were made for multiple comparisons.⁹ An alpha of .05 was set as the level of significance.

Results

Baseline Demographic Information

Of 212 IV tPA-treated patients, 84 (40%) had evidence of prior infarct on pretreatment CT. Lacunes were seen in 55 patients (26%), whereas 47 patients (22%) had evidence of prior cortical strokes. Both lacunar and cortical infarcts were found in 17 patients (8%). Patients with prior infarcts on CT were older (mean age, 72 versus 65 years; $P = .001$), were more likely to have a history of hypertension (85% versus 71%; $P = .024$) or congestive heart failure (19% versus 9%; $P = .026$), were more often on antiplatelet agents before admission (49% versus 31%; $P = .007$), and had higher pretreatment NIHSS scores (median, 10 versus 7; $P = .023$). Demographic variables are fully listed in Table 1 for the dichotomized groups.

Stroke Outcomes

As shown in Table 2, patients with prior infarcts on CT did not experience significantly more sICH (4% versus 2%; $P = .221$) or HT of any type (18% versus 14%; $P = .471$). Patients with evidence of prior stroke on pre-treatment CT were discharged to home or inpatient rehabilitation center less often, albeit not statistically significantly (61% versus 73%; $P = .065$), and had higher frequencies of poor functional outcome at discharge (82% versus 50%; $P < .001$).

We did not find any differences in the frequencies of sICH, HT of any type, or discharge disposition when examining outcomes compared with stroke types (lacune versus cortical infarction, Table 3). In the crude logistic regression model assessing odds of any HT, those with evidence of prior stroke on CT were not statistically significantly at higher odds of having an HT (odds ratio [OR], 1.32; 95% confidence interval [CI], .62–2.78; $P = .4716$). In the crude logistic regression model assessing odds of sICH, those with evidence of prior stroke on CT were not statistically significantly at higher odds of having an sICH (OR, 2.32; 95% CI, .38–14.2; $P = .3637$). However, in the crude model those with evidence of prior stroke on CT were at greater odds for being discharged with poor functional outcomes (OR, 4.7; 95% CI, 2.12–10.5; $P = .0001$). Adjusting for baseline NIHSS score, age, antiplatelet medication use, and history of hypertension, those with evidence of prior stroke on CT remain at greater odds for being discharged with poor functional outcomes (OR, 3.89; 95% CI, 1.62–9.36; $P = .0024$). Compared with patients without prior lacunes, patients with lacunar infarctions more often had an unfavorable functional outcome (78% versus 57%; $P = .006$). Similarly, unfavorable functional outcomes were seen in patients with prior cortical infarctions compared with those without (85% versus 56%; $P = .001$).

Discussion

Patients with prior infarcts on initial head CT were common during the evaluation of acute stroke patients (2 of 5) but do not appear to be at increased risk of sICH after tPA administration. Given that the annual stroke recurrence rate can vary between 5% and 20%,^{10,11} it is not surprising that nearly 40% of our patients had evidence of prior infarcts. In addition, many patients may not be aware of a previous stroke because the prevalence of silent infarcts has been shown to be approximately 10%¹² or even higher in at risk populations (13%–58%).^{12–14} It is encouraging, however, that despite this high frequency of prior infarcts, our results illustrate that patients with evidence of prior infarct on CT do not have higher frequencies of any HT, and more importantly sICH, compared with patients without evidence of prior infarct. The frequency of sICH (2.4%) at our center was higher than what has been reported in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (1.7%),⁸ and it was less than what has been reported in the literature from Get with the Guidelines (4.8%)¹⁵; however, our definition of sICH is more broad than what was used in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study and Get with the Guidelines, which could inflate our frequency of sICH.

Previously, several studies have addressed the question of tPA safety in patients with a clinical history of stroke. The subgroup analysis of the National Institute of Neurological Disorders and Stroke tPA trial demonstrated that tPA was safe in the subgroup of patients who have had a prior stroke.¹⁶ Although patients with concurrent diabetes and history of prior stroke were excluded from the European Cooperative Acute Stroke Study 3,¹⁷ further research has shown that these patients are not at increased risk of sICH when treated with tPA, and that these patients have better outcomes than controls who were not treated with tPA.¹⁸ Recently, it has been demonstrated that the presence of clinically silent infarcts on pretreatment MRI does not increase the risk of sICH.¹⁹ Similarly, our data suggest that patients with evidence of any prior infarct on CT may be safely treated.

Despite prior infarctions not being associated with sICH, we found a relationship between prior infarct and poor functional outcome at discharge, consistent with previous reports.²⁰ This may partially be because of the pre-existing functional deficits of patients with prior stroke. Unfortunately, pretreatment modified Rankin Scale scores were not available to allow us to examine this association.

When we analyzed outcomes relative to the type of stroke seen on pretreatment CT imaging, we found that sICH frequencies did not change significantly based on the presence of prior cortical infarcts or lacunes. We found similar results for functional outcome. Palumbo et al²¹ described the presence of multiple lacunes as not related to poor clinical outcome at 90 days; however, contrary to our data, their study found an increase in sICH in patients with prior lacunes. Many of these patients also had extensive leukoaraiosis that may increase the risk of sICH.²² Unlike their study, we did not further divide patients based on the number of prior lacunes. This may contribute to some of the differences seen between our results and that reported by Palumbo et al.

Our study is not without limitations. This is a retrospective review of data collected from a single academic center prospective stroke registry. Moreover, the practices at our center, particularly rates of tPA administration (30%) may not reflect the general practice.^{23,24} The sample size may limit our ability to detect existing differences between groups. Our data does not describe infarct volume or the number of previous infarcts seen on previous imaging. We were not able to adjust for time from the onset to tPA treatment in our adjusted analyses. We were unable to acquire more than short-term outcomes; however, disability status at discharge has been shown to be a significant predictor of functional outcome at 90 days.²⁵

In our sample, prior infarct on pretreatment CT did not result in significantly higher frequencies of HTor sICH after IV tPA. Our data suggest that prior infarcts on CT should not be viewed as a reason to withhold this treatment after a recent infarct (ie, within 3 months) has been ruled out based on available pretreatment information.

Acknowledgments

Dr Albright is supported by award numbers 5 T32 HS013852-10 from the Agency for Healthcare Research and Quality, 3 P60 MD000502-08S1 from the National Institute on Minority Health and Health Disparities, and the National Institutes of Health. Ms Boehme is supported by award 13PRE13830003 from the American Heart Association.

References

1. Tissue plasminogen activator for acute ischemic stroke; The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995; 333:1581–1587. [PubMed: 7477192]
2. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke*. 1997; 28:2109–2118. [PubMed: 9368550]
3. Derex L, Hermier M, Adeleine P, et al. Clinical and imaging predictors of intracerebral haemorrhage in stroke patients treated with intravenous tissue plasminogen activator. *J Neurol Neurosurg Psychiatry*. 2005; 76:70–75. [PubMed: 15607998]

4. Selim M, Fink JN, Kumar S, et al. Predictors of hemorrhagic transformation after intravenous recombinant tissue plasminogen activator: prognostic value of the initial apparent diffusion coefficient and diffusion-weighted lesion volume. *Stroke*. 2002; 33:2047–2052. [PubMed: 12154261]
5. Kufner A, Galinovic I, Brunecker P, et al. Early infarct FLAIR hyperintensity is associated with increased hemorrhagic transformation after thrombolysis. *Eur J Neurol*. 2013; 20:281–285. [PubMed: 22900825]
6. Patel SC, Levine SR, Tilley BC, et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA*. 2001; 286:2830–2838. [PubMed: 11735758]
7. Kharitonova T, Ahmed N, Thoren M, et al. Hyperdense middle cerebral artery sign on admission CT scan—prognostic significance for ischaemic stroke patients treated with intravenous thrombolysis in the safe implementation of thrombolysis in Stroke International Stroke Thrombolysis Register. *Cerebrovasc Dis*. 2009; 27:51–59. [PubMed: 19018138]
8. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007; 369:275–282. [PubMed: 17258667]
9. Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol*. 2001; 54:343–349. [PubMed: 11297884]
10. Hong KS, Yeghian S, Lee M, et al. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. *Circulation*. 2011; 123:2111–2119. [PubMed: 21536995]
11. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011; 123:e18–e209. [PubMed: 21160056]
12. Kase CS, Wolf PA, Chodosh EH, et al. Prevalence of silent stroke in patients presenting with initial stroke: the Framingham Study. *Stroke*. 1989; 20:850–852. [PubMed: 2749843]
13. Kempster PA, Gerraty RP, Gates PC. Asymptomatic cerebral infarction in patients with chronic atrial fibrillation. *Stroke*. 1988; 19:955–957. [PubMed: 3400107]
14. Petersen P, Madsen EB, Brun B, et al. Silent cerebral infarction in chronic atrial fibrillation. *Stroke*. 1987; 18:1098–1100. [PubMed: 3686584]
15. Menon BK, Saver JL, Prabhakaran S, et al. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator. *Stroke*. 2012; 43:2293–2299. [PubMed: 22811458]
16. Subgroup analysis of the NINDS t-PA stroke trial. Generalized efficacy of t-PA for acute stroke. *Stroke*. 1997; 28:2119–2125. [PubMed: 9368551]
17. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008; 359:1317–1329. [PubMed: 18815396]
18. Mishra NK, Ahmed N, Davalos A, et al. Thrombolysis outcomes in acute ischemic stroke patients with prior stroke and diabetes mellitus. *Neurology*. 2011; 77:1866–1872. [PubMed: 22094479]
19. Tisserand M, Le Guennec L, Touze E, et al. Prevalence of MRI-defined recent silent ischemia and associated bleeding risk with thrombolysis. *Neurology*. 2011; 76:1288–1295. [PubMed: 21389281]
20. Demchuk AM, Tanne D, Hill MD, et al. Predictors of good outcome after intravenous tPA for acute ischemic stroke. *Neurology*. 2001; 57:474–480. [PubMed: 11502916]
21. Palumbo V, Boulanger JM, Hill MD, et al. Leukoaraiosis and intracerebral hemorrhage after thrombolysis in acute stroke. *Neurology*. 2007; 68:1020–1024. [PubMed: 17389306]
22. Neumann-Haefelin T, Hoelig S, Berkefeld J, et al. Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. *Stroke*. 2006; 37:2463–2466. [PubMed: 16931786]
23. Kleindorfer D, Lindsell CJ, Brass L, et al. National US estimates of recombinant tissue plasminogen activator use: ICD-9 codes substantially underestimate. *Stroke*. 2008; 39:924–928. [PubMed: 18239184]

24. Reeves MJ, Arora S, Broderick JP, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke*. 2005; 36:1232–1240. [PubMed: 15890989]
25. Ovbiagele B, Saver JL. Day-90 acute ischemic stroke outcomes can be derived from early functional activity level. *Cerebrovasc Dis*. 2010; 29:50–56. [PubMed: 19893312]

Table 1

Baseline demographic information for patients with and without prior strokes

Variable	No prior stroke (N = 128)	Prior stroke (N = 84)	P value
Male gender, %	53% (68)	57% (48)	.565
Age (range), y	65 (25–99)	72 (24–96)	.001
Race			.107
White	66% (85)	52% (44)	
Black	32% (41)	46% (39)	
Past medical history			
Diabetes	24% (31)	29% (24)	.479
Hypertension	71% (91)	85% (71)	.024
Dyslipidemia	33% (42)	30% (25)	.640
Atrial fibrillation	19% (24)	21% (18)	.632
Congestive heart failure	9% (11)	19% (16)	.026
Medications			
Oral DM medications	17% (22)	13% (11)	.421
Antihypertensives	57% (73)	70% (59)	.052
Antiplatelet agents	31% (39)	49% (41)	.007
Warfarin	4% (5)	7% (6)	.350
Dabigatran	0% (0)	1% (1)	.396
Current smoker	30% (38)	26% (22)	.580
IA treatment used	2% (3)	3% (2)	1.000
NIHSS on admission (range)	7 (0–23)	10 (0–32)	.023

Abbreviations: DM, diabetes mellitus; NIHSS, National Institutes of Health Stroke Scale.

Table 2

Outcomes of patients with and without prior stroke

Variable	No prior stroke	Prior stroke	<i>P</i> value
Symptomatic intracerebral hemorrhage	2% (2/127)	4% (3/84)	.221
Any hemorrhagic transformation	14% (18/127)	18% (15/84)	.471
Discharge to home or inpatient rehabilitation center	73% (88/120)	61% (49/81)	.065
Discharge modified Rankin Scale score 3–6	50% (62/125)	82% (69/84)	<.001

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Outcomes in patients with prior lacunes or cortical strokes

Outcome variable	No prior lacune	Prior lacune	P value	No prior cortical stroke	Prior cortical stroke	P value
Symptomatic intracerebral hemorrhage	2% (3/156)	4% (2/55)	.473	2% (4/163)	2% (1/47)	.897
Any hemorrhagic transformation	14% (22/156)	20% (11/55)	.301	15% (25/163)	17% (8/47)	.780
Discharge to home or inpatient rehabilitation center	69% (101/146)	66% (36/55)	.613	71% (111/156)	57% (25/44)	.156
Discharge modified Rankin Scale score 3–6	57% (88/154)	78% (43/55)	.006	56% (90/161)	85% (40/47)	.001