Impact of Protocol Deviations in Acute Ischemic Stroke Treated With Intravenous rt-PA Within 4.5 Hours After Symptom Onset

Y. J. Alderazi, MB, BCh¹, J. Chang, MD², J. P. Yang, MD³, M. Teleb, MD⁴, K. Chapple, PhD², A. Awad⁵, and Lucas Restrepo, MD, PhD⁶

Abstract

Background: There is limited experience in the community with intravenous tissue plasminogen activator (rt-PA) administered 3 to 4.5 hours after acute ischemic stroke (AIS) onset. Many patients do not meet entry criteria of pivotal clinical trials because of severe stroke, age >80, severe hypertension (sHTN), or history of previous stroke and diabetes. Whether rt-PA benefits these patients is unclear. Thus, we investigated the outcomes of stroke patients treated with rt-PA with or without these adverse clinical characteristics. **Methods:** Chart review of patients with AIS treated with intravenous rt-PA at a single institution. Outcomes at discharge were compared between patients with severe stroke, age >80, sHTN, or previous stroke/diabetes and those without these characteristics. Good outcome was defined as modified Rankin score (mRS) of 0 to 1. Analysis of variance and t tests were used to compare the outcomes. **Results:** Of the 118 cases analyzed, 103 (87%) were treated ≤ 3 hours and 15 (13%) between 3 and 4.5 hours. Sixty-three (53%) patients had severe stroke, age >80, sHTN, or previous stroke/diabetes, whereas 55 (47%) did not. Compared to controls, patients with these adverse characteristics were less likely to have good outcomes (35% vs 56%, $p = .02$). No patients treated within the 3- to 4.5-hour window experienced symptomatic intracranial hemorrhage (sICH). Eight patients treated between 3 and 4.5 hours had severe stroke, age >80, sHTN, or previous stroke/diabetes. Of these, 6 had poor outcomes. **Conclusions:** In a highly selected group of patients treated with intravenous rt-PA, lack of adherence to current guidelines did not improve stroke outcomes. This was related to more severe strokes at baseline, not sICH. Prospective studies of this patient group are needed.

Keywords

stroke, cerebrovascular disorders, outcomes, techniques, safety, techniques, quality, techniques

Background

Therapy with intravenous tissue plasminogen activator (rt-PA) increases the chance of complete recovery in patients with acute ischemic stroke (AIS). However, many patients are not eligible for this therapy because of several relative contraindications, which are derived from the exclusion and inclusion criteria of pivotal clinical trials. Although patients treated within 90 minutes of symptom onset profit the most from this therapy, pooled analysis from stroke trials showed potential benefit of therapy beyond 3 hours.¹ The ECASS-3 trial confirmed this benefit, although resorting to additional exclusion criteria.^{2,3} A recent analysis of the International Stroke Thrombolysis Registry (SITS-ISTR) and meta-analysis of randomized-controlled trials showed comparable efficacy and safety outcomes between patients treated <3 hours and those treated 3 to 4.5 hours after symptom onset.^{4,5} Published guidelines currently recommend the use of

intravenous rt-PA in patients with AIS presenting within 4.5 hours after symptom onset.⁶ However, it is unclear which risk factors tip the balance between efficacy and harm in patients

¹ Department of Neurology, University of Texas Houston, TX, USA

² Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

³ Department of Neurology, Duke University Medical Center, Durham, NC, USA

⁴ Department of Neurology, Stanford University Medical Center, Palo Alto, CA, USA

⁵ Arizona State University, Tempe, AZ, USA

⁶ Department of Neurology, UCLA Medical Center, Los Angeles, CA, USA

Corresponding Author:

Lucas Restrepo, MD, PhD, Comprehensive Stroke and Vascular Neurology Program, Department of Neurology, University of California, Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095, USA
Email: lrestrepo@ucla.edu

treated 3 to 4.5 hours. In particular, many patients in the community would not meet ECASS-3 entry criteria, because of severe stroke, age >80, severe hypertension (sHTN), or history of previous stroke and diabetes.^{7,8} The lack of alternatives to intravenous fibrinolysis has persuaded many physicians, including ourselves, to offer this treatment to an increasing number of patients with AIS presenting with such clinical characteristics. In view of this uncertainty, we examined the clinical characteristics and early outcomes of patients with AIS treated with intravenous rt-PA at our institution within 4.5 hours after the onset of symptoms. In particular, we investigated whether patients with severe stroke, age >80, sHTN, or history of previous stroke and diabetes benefited from treatment.

Methods

Patients

We retrospectively reviewed the charts of all patients with AIS treated with intravenous rt-PA at the Barrow Neurological Institute between January 2007 and July 2009. This institution is a 697-bed medical center that serves as a major primary and referral center for stroke in the city of Phoenix, Arizona. Chart review was approved by the local institutional review board. Informed consent was not obtained in any of the patients receiving intravenous rt-PA, including instances when intravenous rt-PA was administered off-label. Under such circumstances, treatment was strictly guided by the clinical judgment of the attending physician overseeing each case; discussions between physicians and patients (or proxy) about the pros and cons of treatment were invariably documented in the charts.

Patients were divided in 2 groups: (1) those treated within 3 hours of symptom onset and (2) those treated 3 to 4.5 hours after symptom onset. We further subdivided each group into group A, patients with any of the following clinical characteristics: severe stroke (National Institutes of Health Stroke Scale [NIHSS] >25), age >80, sHTN (systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive IV treatment to reduce blood pressure [BP] to these limits), or history of previous stroke and diabetes, and group B constituted by patients without these characteristics (ie, patients who would be enrolled in ECASS-3 if therapeutic window was 3 to 4.5 hours). All patients were assessed in the emergency room by a stroke neurologist or by a neurology resident in consultation with a stroke neurologist.

All patients met the following criteria: (a) AIS diagnosis with known time of onset, (b) acute focal neurological deficit, (c) BP <185/110 mm Hg, or treatment initiated to lower BP prior to fibrinolysis, (d) computed tomography (CT) scan not showing intracranial hemorrhage (ICH) or hypodensity >1/3 of MCA territory. Patients rapidly improving or having minor symptoms were included, as well as those receiving warfarin if the international normalized ratio [INR] was ≤ 1.7 . Patients

with endovascular interventions after intravenous rt-PA, patients without known time of onset, and stroke mimics were excluded. For determination of ischemic stroke subtype, the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria were used.⁹

Treatment

All patients were treated with standard dose intravenous rt-PA 0.9 mg/kg with 10% given as initial bolus and remainder given over 1 hour. Further care was provided by the stroke team in the neurological intensive care and stroke units.

Baseline Data

Baseline data collected for patients included age, gender, ethnicity, time of onset, door-to-needle time, history of vascular risk factors, NIHSS score, modified Rankin scale (mRS), BP measurements, antiplatelet use, statin use, and baseline laboratory testing.

Outcome Assessment

Clinical outcomes were defined as good if the mRS was 0 or 1 at discharge, and poor if the mRS was 2 or greater at discharge from the hospital. The NIHSS at discharge was abstracted from the clinical record.¹⁰ Safety was assessed by the development of symptomatic ICH defined as any ICH associated with a >4-point increase in the NIHSS. Good discharge disposition was defined as discharge to home or acute rehab. Outcomes were deduced from charts and abstracted by the first author (Y.J.A.).

Statistical Analysis

Two-tailed independent sample *t* tests were used to compare means between groups, and analysis of variance (ANOVA) was used for testing for differences between more than 2 groups. Significant differences were deemed present when the *P* value was <.05. The Kruskal-Wallis Test was used when testing for difference across all 4 groups. Mann-Whitney *U* test was used for follow-up comparisons. The Bonferroni method was used to control for type I errors with significance adjusted to *P* value of less than .008. Logistic regression was used to test relations between each of the ECASS-3 criteria and outcomes. SPSS was used for data analysis.

Results

A total of 163 patients were identified; of these, 24 were excluded from final analysis because of endovascular interventions after intravenous rt-PA, while 21 were excluded because of unknown time of symptom onset. A total of 118 patients met our exclusion and inclusion criteria: 103 (87%) treated within 3 hours after symptom onset and 15 (13%) between 3 and 4.5 hours. Out of the entire cohort, 63 (53%)

Table 1. Demographic and Baseline Characteristics of the Patients

Characteristic	Group B, n = 55	Group A n = 63	P Value
Age, mean (SD)	63.8 (11.0)	73.4 (15.2)	<.001
Time to treatment initiation	143.0 (41.8)	134.3 (40.9)	ns
NIHSS	8.0 (6.2)	12.3 (8.9)	<.01
Systolic BP	147.2 (23.3)	174.3 (29.8)	<.01
Diastolic BP	81.8 (15.3)	91.8 (18.3)	<.001
Admission glucose	145.1 (63.0)	163.7 (94.0)	ns
Weight, kg	83.8 (22.0)	80.3 (18.0)	ns
Male (%)	34 (61.8%)	29 (46.0%)	ns
History of stroke	16 (29.1%)	23 (36.5%)	ns
Atrial fibrillation	4 (7.3%)	22 (34.9%)	<.001
History of hypertension	43 (78.2%)	48 (76.2%)	ns
Diabetes mellitus	18 (32.7%)	26 (41.3%)	ns
Coronary artery disease	18 (32.7%)	14 (22.2%)	ns
Congestive heart failure	9 (16.4%)	12 (19.0%)	ns
Hyperlipidemia	39 (70.9%)	36 (57.1%)	ns
Statin use	22 (40.0%)	21 (33.3%)	ns
Antiplatelet use	23 (41.8%)	29 (46.0%)	ns
Tobacco smoking	24 (46.2%)	19 (31.7%)	ns
ECASS-3 criteria			
Severe hypertension	0	25 (39.7%)	
Age >80 years	0	30 (47.6%)	
Anticoagulation, INR >1.7	0	0	
Baseline NIHSS >25	0	8 (12.7%)	
Previous stroke and diabetes	0	24 (38.1%)	

Abbreviations: BP, blood pressure; SD, standard deviation; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale.

patients had severe stroke, age >80, sHTN, or history of previous stroke and diabetes (group A), while 55 (47%) did not have any of these characteristics (group B). These 2 groups were similar with regard to baseline clinical characteristics, except for history of hypertension and atrial fibrillation (Table 1).

Group B patients were more likely to have a good outcome than their group A counterparts (56% vs 35%, respectively, $P = .02$; Figure 1). Group B patients treated ≤ 3 hours after symptom onset had lower mRS at hospital discharge than group A patients treated ≤ 3 hours (median mRS 1 vs 3, respectively, $P = .002$; Figure 1). Analysis also revealed that patients not taking antiplatelet agents prior to stroke onset were more likely to have a poor outcome (44% vs 64%; $P < .05$). On average, lower weight was associated with poor outcome; as was higher initial systolic BP.

Death occurred in 8 (6.8%) patients, 6 of whom belonged to Group A. None of the patients treated between 3 and 4.5 hours after symptom onset experienced symptomatic ICH, although 2 (13%) patients had asymptomatic hemorrhagic transformation. In contrast, 3 (2.9%) patients treated within the 3-hour window developed symptomatic ICH, 2 of whom were taking antiplatelets before stroke onset. ECASS-3 criteria was not met in 8 (53%) of 15 patients treated between 3 and 4.5 hours (4 had sHTN, 2 were octogenarian, 2 had initial NIHSS >25, and 1 had previous stroke and diabetes). Of these 8 patients, 6 (75%) had poor outcome. In contrast, 3 (43%) out of 7 patients meeting ECASS-3 criteria had poor outcome, but the

difference was not significant ($P = .5$). The length of stay in the hospital was 5.7 ± 4.37 days for all groups.

Logistic regression analysis showed that sHTN was an important predictor of poor outcome (odds ratio [OR] 3.0; 95% confidence interval [CI] 1.11-8.08). The NIHSS >25 was associated with decreased odds of being discharged to home or to acute rehabilitation (OR 0.14; 95% CI 0.03-0.67). However, NIHSS >25, age >80, sHTN, or history of previous stroke and diabetes were not associated with ICH in this cohort (regardless of therapeutic window).

Discussion

This single-center analysis of patients with AIS treated with intravenous rt-PA suggests that, regardless of time to treatment, NIHSS >25, age >80, sHTN, or history of previous stroke and diabetes was associated with poor AIS outcomes. This data suggests that breaching of the ECASS-3 selection criteria did not benefit patients treated between 3 and 4.5 hours after symptom onset in the studied cohort. Furthermore, intravenous rt-PA did not lead to complications that exacerbated stroke severity in this patient cohort; in particular, symptomatic ICH was not responsible for the observed outcome differences. In fact, our regression analysis suggests that lack of efficacy of intravenous rt-PA in group A patients was related to observed differences in initial stroke severity and sHTN. Additional clinical characteristics, including history of atrial fibrillation, use of antiplatelet agents prior to stroke,

Figure 1. The distribution of modified Rankin scores (mRS) is shown for the 4 patient populations based on the presence of clinical characteristics (group A vs group B) and time from onset to treatment (≤ 3 hours vs 3-4.5 hours). Overall, patients in group B were more likely to have a good outcome than patients in group A (56% vs 35%, respectively, $P = .02$). Group B patients treated ≤ 3 hours had lower mRS at hospital discharge than group A patients treated ≤ 3 hours (median mRS 1 vs 3, respectively, $P = .002$). ^a Group A: patients with NIHSS >25 , age >80 , systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or history of both stroke and diabetes mellitus. ^b There were no patients with mRS of 0, 2, or 5 in this group.

and lower body weight, may have also played a role. However, a meaningful increase in symptomatic ICH risk may have been missed due to lack of study power. The observation of lower weight being associated with a poor outcome is interesting, in light of recent data linking obesity to early survival rates after stroke.¹¹

This study has some limitations which need to be cautiously considered before interpreting the results. These include its retrospective design, which can distort our findings; the relatively small number of patients treated within the 3 to 4.5 hours window, which can introduce a type II error; and the possibility of having a selection bias, as many patients were excluded from our analysis because of treatment outside of established guidelines (ie, many cases treated with endovascular techniques or combined intravenous and intra-arterial delivery of fibrinolytics). Presumably, these patients had more severe strokes. Another study limitation is that our outcomes are based on mRS gathered at the time of discharge from the hospital rather than 90 days after stroke onset. Hence, we did not measure the full extent of functional improvement in our patients, as mRS at 90 days would likely be better 90 days after hospital discharge. Patients not meeting ECASS-3 criteria also had higher prevalence of atrial fibrillation at baseline, a factor commonly associated with severe strokes and poor outcomes.¹² Age and initial stroke severity were different between groups, but this was expected as both variables are part of ECASS-3 entry criteria. Consequently, our results require independent confirmation, preferably through a prospective, controlled trial.

This study highlights 2 clinical problems that deserve further investigation: first, relevant ECASS-3 exclusion criteria

(NIHSS >25 , age >80 , sHTN, and previous stroke and diabetes) are factors deemed to reduce intravenous rt-PA efficacy and increase the risk of symptomatic ICH. Hence, alternatives to intravenous rt-PA may be necessary for patients with these clinical characteristics. Second, ECASS-3 criteria may deprive some patients from the benefits of intravenous fibrinolysis, which is illustrated by our 2 patients treated within 3 to 4.5 hours who did not meet the criteria for ECASS-3 entry but had excellent outcomes.

The off-label use of intravenous rt-PA may be justified on the basis of lack of widely available alternatives for AIS treatment. In the absence of controlled, randomized trials evaluating rt-PA efficacy in relevant clinical scenarios (ie, octogenarians, etc), the best approximation will depend on the clinical judgment of treating physicians, keeping in mind the results of small-scale studies like ours. We suggest that the off-label use of intravenous rt-PA must be discussed candidly with patients and family, indicating that rt-PA has not been studied in the particular situation in which it is being offered. This conversation has to include the possibility of inefficacy and stroke worsening with or without symptomatic ICH. Once the decision is made to use off-label rt-PA, some interventions may help improve outcomes, including observation in a neurocritical care/stroke unit, avoidance of anticoagulants immediately after rt-PA administration, prescribing statins, treating medical complications aggressively, and preventing stroke recurrence. Although sHTN was associated with poor outcomes in the studied cohort, this was not related to symptomatic ICH. It remains unclear whether strict control of BP may improve outcomes after intravenous fibrinolysis or

whether sHTN simply represents a marker of severe strokes in general, demanding caution from the clinician.

We conclude that severe stroke, age >80, sHTN, and history of previous stroke and diabetes were associated with poor outcomes in a highly selected cohort of patients with AIS. While the clinical benefit of treating patients 3 to 4.5 hours after symptom onset is tangible and can be translated to everyday practice, deviations from existing treatment guidelines may not improve stroke outcomes.^{13,14} However, the potential of offering treatment to more stroke patients presenting beyond the 3-hour window using less stringent eligibility criteria merits further investigation. A large multicenter prospective study of patients with relative contraindications for intravenous rt-PA is warranted, given the increasing age of our population and the relatively high prevalence of previous stroke and diabetes in the community. Although the limitations of our study do not allow us to make recommendations regarding the use of intravenous rt-PA in these particular cases, we suggest that institutions interested in stroke care should decide beforehand what to do under such circumstances based on the analysis of their own outcomes, until a suitable study solves this question.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Reference

1. The ATLANTIS, ECASS, NINDS rt-PA Study Group Investigators, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363(9411):768–774.
2. Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317–1329.
3. Saver JL, Gornbein J, Grotta J, et al. Number needed to treat to benefit and to harm for intravenous tissue plasminogen activator therapy in the 3- to 4.5-hour window: joint outcome table analysis of the ECASS 3 trial. *Stroke*. 2009;40(7):2433–2437.
4. Wahlgren N, Ahmed N, Dávalos A, et al; SITS investigators. Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet*. 2008;372(9646):1303–1309.
5. Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to 4.5 hours after acute ischemic stroke: a meta analysis. *Stroke*. 2009;40(7):2438–2441.
6. Del Zoppo GJ, Saver JL, Jauch EC, et al; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40(8):2945–2948.
7. Bluhmki E, Chamorro A, Dávalos A, et al. Stroke treatment with alteplase given 3.0–4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol*. 2009;8(12):1095–1102.
8. Alshekhlee A, Mohammadi A, Mehta S, et al. Is thrombolysis safe in the elderly?: analysis of a national database. *Stroke*. 2010;41(10):2259–2264.
9. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35–41.
10. Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the NIH Stroke Scale. *Stroke*. 2000;31(4):858–862.
11. Vemmos K, Ntaios G, Spengos K, et al. Association between obesity and mortality after acute first-ever stroke. *Stroke*. 2011;42(1):30–36.
12. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation: the copenhagen stroke study. *Stroke*. 1996;27(10):1765–1769.
13. Tung CE, Win SS, Lansberg MG. Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke. *Stroke*. 2011;42(8):2257–2262.
14. Minnerup J, Wersching H, Ringelstein EB, et al. Impact of the extended thrombolysis time window on the proportion of recombinant tissue-type plasminogen activator-treated stroke patients and on door-to-needle time. *Stroke*. 2011;42(10):2838–2843.