Published in final edited form as:

J Stroke Cerebrovasc Dis. 2012 November ; 21(8): 732–736. doi:10.1016/j.jstrokecerebrovasdis.2011.03.009.

Intravenous t-PA for Patients with Minor Ischemic Stroke

Branko N Huisa, M.D.¹, Rema Raman, Ph.D.^{2,3}, Will Neil, M.D.², Karin Ernststrom, MS³, and Thomas M Hemmen, M.D., Ph.D.²

¹University of New Mexico. Neurology Department

²University of California San Diego. Department of Neurosciences

³University of California San Diego, Department of Family and Preventive Medicine

Abstract

Patients with minor ischemic stroke (MIS) are frequently excluded from thrombolytic therapy. Denial of therapy to these patients, however, remains controversial. We compared outcomes in patients with MIS who received IV t-PA with those untreated.

We selected adult patients with stroke onset within 3 hours from a prospectively collected stroke registry. MIS was defined as an admission National Institutes of Health Stroke Scale (NIHSS) score ≤ 5 . The primary outcome was a 90 day mRS of 0–1. Secondary outcomes were Barthel index (BI) ≥ 95 at 90 days, symptomatic intracranial hemorrhage (sICH) and death. Multivariable logistic regression was performed to determine the association between outcomes, adjusting for age, history of diabetes and admission NIHSS. Reasons for t-PA exclusion were obtained.

We identified 133 patients with MIS; 59 patients received IV t-PA. Admission NIHSS was higher in the t-PA treated group (mean $\pm$ SD); 3.4 ± 1.4 ; 1.9 ± 1.3 ; $p < 0.0001$. Other baseline characteristics were not significantly different between groups. At 90 days, 57.6% in the t-PA and 68.9% in the untreated group had a mRS of 0–1 (OR 0.93, 95% CI: 0.39–2.2, $p=0.87$). BI of 95–100 was achieved in 75% of patients in the IV t-PA group vs. 78.9% in the untreated group; (OR 1.18, 95% CI: 0.43–3.23, $p=0.74$). There were 3 deaths (5.1%) in the IV t-PA group vs. 3 (4.1%) in the controls.

In our sample, patients with MIS treated with IV t-PA have similar outcomes as patients not receiving thrombolysis. A randomized trial or larger observational study is needed confirm or reject these findings.

INTRODUCTION

Only 1–8% of all ischemic stroke patients are treated with intravenous t-PA.¹ The most common reason for failure to treat in patients who are otherwise eligible is the treating practitioner's perception that the stroke is too mild or rapidly improving.^{2, 3} The 1995 NINDS t-PA study showed that intravenous (IV) tissue plasminogen activator (t-PA) improves outcomes of patients suffering ischemic stroke who are treated within 3 hours from stroke symptom onset.⁴ The ECASS III study recently expanded this treatment

© 2011 National Stroke Association. Published by Elsevier Inc. All rights reserved.

Address correspondence to: Branko N. Huisa, MD, Department of Neurology, MSC10 5620 HSC 1UNM, Albuquerque, New Mexico 87131, Telephone: (505) 272-3342, Fax: (505) 272-6692, bhuisa@unm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

window to 4.5 hours.⁵ Although both studies excluded patients with mild stroke, they failed to clearly define a certain threshold for a mild deficit. The approval for t-PA by the regulatory bodies in the US (FDA) and Europe (EMA) did not limit its use for patients with mild deficits. Although patient outcome improves with lower pretreatment NIHSS,⁶ a substantial minority of patients deemed too mild for IV t-PA were unable to be discharged home.⁷ We compared clinical and safety outcomes in patients with minor ischemic stroke (MIS), presenting within 3 hours from stroke onset, treated with intravenous t-PA versus those who were not treated.

METHODS

Between January 2005 and June 2010, we selected patients from a prospective stroke database who presented to the emergency department within 3hrs from stroke onset and had an admission National Institutes of Health Stroke Scale (NIHSS) score ≤ 5 . Patients were divided into two groups: 1) patients treated with IV t-PA and 2) patients not given any thrombolytic therapy. Patients treated with intra-arterial t-PA or other experimental therapies were excluded. All patients received a modified Rankin Score (mRS) and Barthel Index (BI) 90 days after the incident stroke. Good outcome was defined as 90 day mRS of 0–1. Secondary outcomes were BI of 95 to 100 at 90 days, symptomatic intracranial hemorrhage (SICH), length of stay (LOS) in the hospital, discharge disposition and death. SICH was defined as any hemorrhage plus any neurological deterioration.⁴ Only patients who received IV t-PA were closely monitored for SICH. The reasons for t-PA exclusion in the untreated group were captured at time of decision making. Our prospective database collection and the study are approved by the University of California San Diego Institutional Review Board.

Statistical analysis

Multivariable logistic regression analysis was performed to determine the association between outcome (Day 90 mRS of 0–1 vs. 2–6, Day 90 BI of <95 vs. 95–100, 90-day mortality) and treatment group, adjusting for age, history of diabetes and initial NIHSS. Group comparisons were performed using Fisher's exact test for categorical variables and Wilcoxon Rank Sum for continuous variables. Since this is an exploratory study, no adjustments were made for multiple comparisons and a p-value of 0.05 was considered to be statistically significant. All statistical analyses were done using R-project version 2.9.1.

RESULTS

We identified 133 patients with MIS; from them, 59 patients received IV t-PA and 74 did not receive any thrombolytic therapy (untreated group). Baseline characteristics (age, gender, race, hypertension, atrial fibrillation, diabetes, tobacco use, pre stroke mRS) were well matched between both groups with the exception of the initial NIHSS (mean $\pm$ SD, median, Q1, Q3); IV t-PA group 3.4 $\pm$ 1.4, 4, 2.5, 5 untreated group 1.9 $\pm$ 1.3, 2, 1, 2; $p < 0.0001$ (Table 1). There was no statistical difference in 90-day outcome. The mRS was 0–1 in 57.6% of the IV t-PA group and 68.9% in the untreated group (adjusted OR 0.93, 95% CI: 0.39–2.20, $p=0.87$). The BI of 95–100 was 75% in the t-PA group and 78.7% in the no t-PA group; (adjusted OR 1.18, 95% CI: 0.43–3.23, $p=0.74$). There were 3 deaths (4.1%) in the untreated group and 3 deaths (5.1%) in the t-PA group ($p>0.99$). There were 3 SICH (5%) in the treatment group. SICH was not obtained in the untreated group. The mean LOS (in days) in the t-PA group was 4.7 (± 4.3) vs. 3.1 (± 2.6) in the untreated group (adjusted $p=0.046$). Most patients in both groups were discharged home; 67.8 % for the t-PA group and 75.7% for the untreated group (adjusted $p=0.67$) (Table 2).

Minor stroke was the only reason for not giving IV t-PA in 33.3% of the untreated group. Other reasons for IV t-PA treatment exclusion were: rapidly improving symptoms 44.6%,

patient or family refusal 8.1%, delay on treatment or out of the window at time of treatment 6.7%, INR>1.7 6.7%, other 4% (Table 3).

DISCUSSION

This study shows no difference in clinical and safety outcomes between MIS patients treated with or without IV t-PA. The rate of SICH, although not registered in the untreated group, was within the expected range and it did not alter the mortality or disability in the treated group. However, because higher NIHSS predicts higher rate of SICH, and few previous studies of minor strokes patients treated with IV t-PA have shown a SICH rates from 0 to 2%^{8,9}, it could be argued that our SICH rate in minor strokes patients was high. Other secondary outcome measurements were similar between groups with the exception of length of hospital stay. Patients treated with t-PA had a longer hospital stay, which contrasts previous cost effectiveness studies that showed shorter length of stay in t-PA treated patients.¹⁰ This may indicate that patients with MIS have very low baseline need for hospital care and that the mandatory monitoring period after t-PA and the treatment related safety concern delay hospital discharge in this population.

Other pilot studies have shown that treatment of MIS patients is feasible and safe.^{9, 11–13} Still, there is disagreement about the use of thrombolytic therapies in these patients; and to date, the answer cannot be derived from randomized controlled trials. Post hoc analyses of the NINDS, ECASS-III trials and outcome in patients from the virtual international stroke trials archive (VISTA), suggest equal efficacy across stroke severity range measured by NIHSS with the exception of patients who fell on the extreme of the scales.¹⁴ Despite of pooling data from VISTA, the power to examine subgroups is lower than chosen for the primary analyses, and patients with MIS were largely under-represented. Nedelchev et al. have shown that mild or rapidly improving stroke patients (NIHSS ≤ 3 or improvement of ≥ 4) have good outcome as defined as mRS ≤ 1 at 90 days. In that study, 75% of MIS or rapidly improving patients had good outcome at 90 days.⁹

We did not include patients with rapidly improving symptoms in our analysis unless the admission NIHSS was ≤ 5. Several other groups have included acute stroke patients with rapidly improving symptoms in the analysis of minor strokes.^{2, 9} Rapidly improving stroke patients frequently show fluctuating symptoms and may represent a different patient population than those with MIS. These patients present with a higher NIHSS, have an unstable clinical picture and poorer outcome if left untreated.² Our case-control study included only MIS from a prospectively collected database, was well matched, and statistically corrected for NIHSS unbalances and variables that could alter outcome.

The limitations of our study are that the sample size is relatively small and derived from a single center experience. Although the results were adjusted for common confounding covariates, the higher NIHSS in the treatment group suggests a selection bias. Regarding the safety analysis, we did not monitor patients who were not treated with IV t-PA for hemorrhage and do not know the SICH and other hemorrhage rate in this group.

Another important limitation of this study resides on the definition of “minor stroke” itself. There is no consensus definition of minor stroke.^{15, 16} The NINDS t-PA trial used “minor stroke” as exclusion criteria, it included 48 patients with NIHSS fewer than 6, and even included patients with NIHSS of 1 and 2.¹⁶ Recently, a study assessed the outcome of minor stroke patients according to 6 different definitions.¹⁵ Having ≥ 1 point on every NIHSS item and normal consciousness or a total NIHSS ≤ 3 resulted in the best outcome measured by mRS 0 to 2 and home disposition after hospitalization.¹⁵ However, minor or zero NIHSS does not assure absence of stroke. Headache, vertigo, nausea, truncal ataxia and

Horner's syndrome constitute alarming symptoms and signs of posterior circulation stroke which are not scored by the NIHSS and could precede a life threatening event if not addressed early.(17) Furthermore, current disability outcome scales such as mRS and BI are likely imperfect, not measuring all the health implications after having a minor stroke.(18) Other outcomes scales such as Stroke Impact Scale (SIS), quality of life (QOL), depression or cognitive scales should be considered in futures studies of MIS patients.

The only way to resolve treatment effect of thrombolytic therapy in MIS patients will be thought a well design randomized clinical trial. However, a venture of such magnitude would be unpractical. First, the treatment effect, if present, is likely to be too small to be detected by the standard stroke outcome measurements, and would require a very large sample. Secondly, only 10% of acute ischemic stroke patients who present to acutely to the emergency department constitute "minor stroke patients", making the recruitment challenging. Furthermore, it is likely that, some physicians will be reluctant to randomize patients based on a NIHSS threshold. Additionally, pre-morbid conditions and patients that overstate symptoms may score more points in the NIHSS. Conversely, it would be unethically to deny treatment to patients with disabling symptoms despite a modest NIHSS. Developing a consensual definition of minor stroke based on disability rather than NIHSS, using new disability scales and maybe adding some imaging biomarkers could be done to overcome these issues.

In conclusion the benefit of thrombolytic therapy for minor strokes remains uncertain. In the absence of a larger randomized trial proving its lack of benefit in minor stroke patients, IV t-PA should be considered in all ischemic stroke patients that fulfill requirements set by current treatment guidelines

Acknowledgments

SOUCE OF FUNDING

Supported by: NIH 3P50 NS044148

REFERENCES

1. Kleindorfer D, Kissela B, Schneider A, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke*. 2004; 35:e27–e29. [PubMed: 14739423]
2. Barber PA, Zhang J, Demchuk AM, et al. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology*. 2001; 56:1015–1020. [PubMed: 11320171]
3. Cocho D, Belvis R, Marti-Fabregas J, et al. Reasons for exclusion from thrombolytic therapy following acute ischemic stroke. *Neurology*. 2005; 64:719–720. [PubMed: 15728300]
4. 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]
5. 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]
6. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1997; 28:2119–2125. [PubMed: 9368551]
7. Smith EE, Abdullah AR, Petkovska I, et al. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. *Stroke*. 2005; 36:2497–2499. [PubMed: 16210552]
8. Baumann CR, Baumgartner RW, Gandjour J, et al. Good outcomes in ischemic stroke patients treated with intravenous thrombolysis despite regressing neurological symptoms. *Stroke*. 2006; 37:1332–1333. [PubMed: 16556881]

9. Nedeltchev K, Schwegler B, Haefeli T, et al. Outcome of stroke with mild or rapidly improving symptoms. *Stroke*. 2007; 38:2531–2535. [PubMed: 17673713]
10. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology*. 1998; 50:883–890. [PubMed: 9566367]
11. Kohrmann M, Nowe T, Huttner HB, et al. Safety and outcome after thrombolysis in stroke patients with mild symptoms. *Cerebrovasc Dis*. 2009; 27:160–166. [PubMed: 19092237]
12. Kruetzelmann A, Siemonsen S, Gerloff C, et al. Thrombolysis targeting MRI defined tissue at risk in minor stroke. *J Neurol Neurosurg Psychiatry*. 2009; 80:1156–1158. [PubMed: 19762906]
13. Steffenhagen N, Hill MD, Poppe AY, et al. Should you thrombolyse all or any stroke patients with baseline National Institutes of Health stroke scale scores < or = 5? *Cerebrovasc Dis*. 2009; 28:201–202.
14. Mishra NK, Lyden P, Grotta JC, et al. Thrombolysis is associated with consistent functional improvement across baseline stroke severity: a comparison of outcomes in patients from the Virtual International Stroke Trials Archive (VISTA). *Stroke*. 41:2612–2617. [PubMed: 20947852]
15. Fischer U, Baumgartner A, Arnold M, et al. What is a minor stroke? *Stroke*. 41:661–666. [PubMed: 20185781]
16. Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience. *Ann Emerg Med*. 2005; 46:243–252. [PubMed: 16126134]
17. Martin-Schild S, Albright KC, Tanksley J, et al. Zero on the NIHSS does not equal the absence of stroke. *Ann Emerg Med*. 57:42–45. [PubMed: 20828876]
18. Duncan PW, Samsa GP, Weinberger M, et al. Health status of individuals with mild stroke. *Stroke*. 1997; 28:740–745. [PubMed: 9099189]

Table 1

Baseline Demographics:

	Untreated, N=74	IV r-tPA, N=59	p
Age	70.1±14.5	66.5±16.4	0.251 [†]
Gender, (Female %)	41.9	39.0	0.859 [†]
Race (%)			0.382 [†]
Asian	2.7	0	
Pacific Islander	0	1.7	
Black	8.1	5.1	
White	89.2	91.5	
Native American	0	1.7	
Baseline NIHSS			
Mean SD	1.9±1.3	3.4±1.4	<0.0001 [‡]
Q1	1	2.5	
Median	2	4	
Q3	2	5	
Diabetes (%)	24.3	18.6	0.528 [†]
A-Fib (%)	23.3	19.6	0.671 [†]
HTN (%)	66.2	59.3	0.471 [†]
Tobacco use (%)	37.8	25.4	0.140 [†]
PreStroke mRS 0-1(%)	87.8	89.8	0.788 [†]

[†]Fisher's Exact[‡]Wilcoxon Rank Sum test.

Table 2

Primary and secondary outcomes.

	Untreated (n=74)	IV – tPA (n=59)	P
Day 90 mRS 0-1(%)	68.9	57.6	0.871 [*]
Barthel Index 95-100 (%)	78.9	75.0	0.740 [*]
Hospitalization days (mean, SD)	3.1±2.6	4.7±4.3	0.046 [‡]
Discharge home (%)	75.7	67.8	0.670 [‡]
Deaths n (%)	3(4.1)	3(5.1)	>0.999 ^{**}
SICH n (%)	Not obtained	3 (5%)	
Any adverse event n(%)	Not obtained	6 (10%)	

[‡] Logistic regression adjusted for Age, baseline NIHSS, Diabetes and prestroke mRS.^{*} Logistic regression adjusted for Age, baseline NIHSS, Diabetes and prestroke mRS.[‡] Linear regression adjusted for Age, baseline NIHSS, Diabetes and prestroke mRS.^{**} Fisher's Exact Test

Table 3

Reasons for IV t-PA treatment exclusion N=74 for minor stroke patients.

Treatment exclusion reason	N (%)
Minor stroke Only	25 (33.7%)
Rapid improving Symptoms *	33 (44.6%)
Patient or family refuse *	6 (8.1%)
INR >1.7 *	5 (6.7%)
>3 hours at treatment time ^{#, *}	5 (6.7%)
Uncontrollable high BP *	1 (1.3%)
Mimic *	1 (1.3%)

* Patients can have more than one treatment exclusion reason.

[#]Time of decision making.