

Safety and Outcomes of Intravenous Thrombolysis in Stroke Mimics

A 6-Year, Single-Care Center Study and a Pooled Analysis of Reported Series

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Background and Purpose—Efforts to increase the availability and shorten the time delivery of intravenous thrombolysis in patients with acute ischemic stroke carry the potential for tissue plasminogen activator administration in patients with diseases other than stroke, that is, stroke mimics (SMs). We aimed to determine safety and to describe outcomes of intravenous thrombolysis in SM.

Methods—We retrospectively analyzed stroke registry data of consecutive acute ischemic stroke admissions treated with intravenous thrombolysis over a 6-year-period. The admission National Institutes of Health Stroke Scale score, vascular risk factors, ischemic lesions on brain MRI (routinely performed as part of diagnostic work-up), and discharge modified Rankin Scale scores were documented. Initial stroke diagnosis in the emergency department was compared with final discharge diagnosis. SM diagnosis was based on the absence of ischemic lesions on diffusion-weighted imaging sequences in addition to an alternate discharge diagnosis. Symptomatic intracranial hemorrhage was defined as brain imaging evidence of intracranial hemorrhage with clinical worsening by National Institutes of Health Stroke Scale score increase of ≥ 4 points.

Results—Intravenous thrombolysis was administered in 539 patients with acute ischemic stroke (55% men; mean age, 66 ± 15 years). Misdiagnosis of acute ischemic stroke was documented in 56 cases (10.4%; 95% CI, 7.9% to 13.3%). Conversion disorder (26.8%), complicated migraine (19.6%), and seizures (19.6%) were the 3 most common final diagnoses in SM. SMs were younger (mean age, 56 ± 13 years) and had milder baseline stroke severity (median National Institutes of Health Stroke Scale, 6; interquartile range, 4) compared with patients with confirmed acute ischemic stroke (mean age, 67 ± 14 years; median National Institutes of Health Stroke Scale, 8; interquartile range, 10; $P < 0.001$). There was no case of symptomatic intracranial hemorrhage in SMs (0%; 95% CI, 0% to 5.5%); 96% of SMs were functionally independent at hospital discharge (modified Rankin Scale, 0 to 1).

Conclusions—Our single-center data indicate favorable safety and outcomes of intravenous thrombolysis administered to SM. (*Stroke*. 2011;42:1771-1774.)

Key Words: intracranial hemorrhage ■ ischemic stroke ■ outcome ■ stroke mimics ■ thrombolysis ■ tPA

The benefit of intravenous thrombolysis (IVT) in patients with acute ischemic stroke (AIS) decreases as time from stroke onset to treatment initiation increases. Consequently, current American Heart Association recommendations advocate that every effort should be taken to shorten delay in

initiation of treatment. However, the efforts to increase the availability of IVT and to reduce the time of delivery of tissue-type plasminogen activator (tPA) carry the potential for administering IVT in patients with a noncerebrovascular etiology for their acute neurological deficits that “mimic”

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Findings of this study have been previously presented (as a podium presentation) at the 2008 International Stroke Conference.

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AIS.^{1,2} Despite the high prevalence of stroke mimics (SMs) among patients presenting acutely to emergency department with suspected or initially diagnosed stroke,³ limited data exist regarding the use of IVT in patients erroneously diagnosed as having AIS in the emergency department.^{4–6} We aimed to determine the safety of thrombolysis and to describe outcomes in SM using the 6-year experience of our tertiary care center and also by performing a pooled analysis of available published data.

Subjects and Methods

Study Population

A retrospective cohort design was used to analyze stroke registry data (Phoenix, AZ) prospectively collected from consecutive AIS admissions treated with 0.9 mg/kg dose of intravenous tPA within 3 hours of stroke onset between January 2003 and December 2008 according to current American Heart Association recommendations. All patients were prospectively identified and their data were entered in a computerized stroke registry. Details about the stroke registry of our institution have been previously described.⁷

On arrival in the emergency department, all patients with acute stroke underwent a standard neurological examination, electrocardiogram, blood chemistry, noncontrast CT, and CT angiogram of the head and neck before tPA administration. Clinical status at baseline was assessed with the National Institutes of Health Stroke Scale (NIHSS) by a certified member of our stroke team. Risk factor identification was performed as previously described.⁷ Pretreatment systolic and diastolic blood pressure levels were measured using automated cuffs. Ischemic lesions on brain MRI (routinely performed as part of diagnostic work-up 24 to 72 hours from symptom onset) were documented from radiology reports. All MRI studies included a diffusion-weighted imaging sequence for assessment of AIS. In patients with contraindications to MRI (eg, pacemaker), a second brain CT was performed within 24 to 72 hours from stroke onset. Initial stroke diagnosis in the emergency department was compared with the final hospital discharge diagnosis. Discharge diagnoses other than AIS were recorded. The conclusion that the presenting symptoms represented SM was based on the absence of ischemic lesions on diffusion-weighted imaging sequences and the presence of an alternate clinical discharge diagnosis.⁶

Symptomatic intracerebral hemorrhage (sICH) was defined as brain imaging evidence of intracerebral hemorrhage with clinical worsening by NIHSS score increase of ≥ 4 points. Functional independence at hospital discharge was assessed using the modified Rankin Scale score (Grades 0 to 1). The length of acute hospital stay (not including any time spent in a subsequent inpatient rehabilitation facility), potential complications during hospitalization, and NIHSS score at hospital discharge were documented in all patients. Neurological improvement during hospitalization was evaluated as the decrease in NIHSS score at discharge from the baseline NIHSS score.

Search Strategy and Data Extraction of Previous Studies

We sought all available previously published studies in which the safety of IVT was evaluated in SMs. Briefly, studies were identified by 2 independent observers (G.T., A.V.A.) from PubMed, Embase, and Cochrane databases (search years January 1996 to July 2010). In the first extraction step, we used the following search terms: “stroke mimic” (289 publications) OR “misdiagnosis of stroke” (1423 publications). In the second extraction step, we added the following search terms: “thrombolysis” and/or “tissue plasminogen activator.” We found 10 publications for “stroke mimic AND thrombolysis,” 4 for “stroke mimic AND tissue plasminogen activator,” 31 for “misdiagnosis of stroke AND thrombolysis,” and 21 for “misdiagnosis of stroke AND tissue plasminogen activator.” In the third extraction step, we identified all studies in which SMs were treated with IVT ($n=4$)^{2,4–6} after excluding case reports ($n=2$). We also

Table 1. Baseline Characteristics and Outcome Variables in SM and in Patients With Confirmed AIS

Variable	SM (n=56)	Confirmed AIS (n=483)	P
Mean age, y (SD)	56 \pm 13	67 \pm 14	<0.001
Male gender	45%	56%	0.096
Median admission NIHSS score, points (IQR)	6 (4–8)	8 (4–14)	<0.001
Median onset-to-treatment time, minutes (IQR)	135 (107–170)	125 (99–162)	0.885
Hypertension	55%	64%	0.229
Diabetes mellitus	14%	25%	0.079
Hypercholesterolemia	52%	37%	0.030
Atrial fibrillation	11%	30%	0.002
Current smoking	32%	33%	0.858
Mean pretreatment SBP, mm Hg (SD)	140 \pm 22	154 \pm 34	0.002
Mean pretreatment DBP, mm Hg (SD)	79 \pm 14	81 \pm 20	0.401
Median pretreatment blood glucose, mg/dL (IQR)	107 (97–121)	125 (106–162)	0.001
sICH, 95% CI	0%*	5%	0.155†
Orolingual edema	0%*	1%	0.719†
Deep venous thrombosis	0%	1%	0.644†
Aspiration pneumonia	0%	5%	0.160†
Median length of hospitalization, d (IQR)	3 (2–5)	5 (3–7)	<0.001
Median neurological improvement, ‡ points (IQR)	6 (3–8)	3 (1–5)	<0.001
Functional independence at hospital discharge§	96%	35%	<0.001†

SM indicates stroke mimic; AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; sICH, symptomatic intracerebral hemorrhage.

*Adjusted Wald 95% CI, 0% to 5.5%.

†Fisher exact test.

‡During hospitalization.

§Modified Rankin Scale score 0 to 1.

searched the bibliographies of all included studies and any relevant review or editorial articles for additional suitable studies.

Statistical Analyses

Continuous variables are presented as mean \pm SD (normal distribution) and as median with interquartile range (skewed distribution). Categorical variables are presented as percentages with corresponding 95% CIs. The adjusted Wald method, which provides the best coverage for binomial CI when samples are less than approximately 150,⁸ was used for computation of 95%CI of sICH prevalence among SMs in our pooled analysis. Statistical comparisons were performed between SMs and patients with confirmed AIS using the χ^2 test, Fisher exact test, unpaired *t* test, and Mann–Whitney *U* test as indicated for dichotomous or continuous variables. The Statistical Package for Social Science (SPSS Inc, Version 11.5 for Windows) was used for statistical analyses.

Results

A total of 539 patients with AIS (55% men; mean age, 66 \pm 15 years; median admission NIHSS score, 8 points; interquartile

Table 2. Definitions and Discharge Diagnosis of SM Among Patients Treated With IVT Across Different Stroke Registries

Registry	SM (No.)	Setting	SM Definition	Alternate Discharge Diagnosis
Michigan ⁴	6	Tertiary care center	Alternate clinical discharge diagnosis*	CD (67%), SZ (17%), MG (17%)
Basel ⁵	7	Tertiary care center	Absence of ischemic lesions on post-tPA MRI/CT† and alternate clinical discharge diagnosis	CD (14%), SZ (86%)
Houston ⁶	69	Tertiary care center	Absence of ischemic lesions on post-treatment MRI (DWI sequences) and alternate clinical discharge diagnosis	CD (21%), SZ (38%), MG (37%)‡
Pittsburgh ²	9	Tertiary care center	Absence of ischemic lesions on post-treatment MRI (DWI sequences) and persistence of neurological symptoms or alternate clinical discharge diagnosis	CD (78%), SZ (22%)
Phoenix	56	Tertiary care center	Absence of ischemic lesions on post-tPA MRI (DWI sequences) and alternate clinical discharge diagnosis	CD (27%), SZ (20%), MG (20%)§

SM indicates stroke mimic; IVT, intravenous thrombolysis; tPA, tissue-type plasminogen activator; DWI, diffusion-weighted imaging; CD, conversion disorder; SZ, seizure; MG, migraine.

*Brain MRI was performed in 3 patients and brain CT in 1 patient after intravenous thrombolysis. There was no post-treatment brain imaging study in 2 cases.

†Brain MRI was performed in 6 patients and contrast-enhanced brain CT in 1 patient after intravenous thrombolysis.

‡Epidural spinal mass (1%), syncope (1%), heat stroke (1%), and aseptic meningitis (1%) included the remaining discharge diagnoses.

§Syncope (9%), acute confusional state (9%), vestibular disorder (5%), meningioma (4%), alcohol intoxication (4%), trochlear nerve palsy (2%), and multiple sclerosis (2%) included in the remaining discharge diagnoses.

range, 5 to 14) fulfilled the inclusion criteria during the 6-year study period. The median elapsed time from symptom onset to tPA infusion was 128 minutes (interquartile range, 100 to 165 minutes). Misdiagnosis of ischemic stroke was documented in 56 of the 539 cases (10.4%; 95% CI, 7.9% to 13.3%). Conversion disorder (26.8%), complicated migraine (19.6%), and seizures (19.6%) were the 3 most common alternate diagnoses in SMs treated with IVT.

Baseline characteristics and outcomes between SMs (n=56) and patients with confirmed AIS (n=483) are compared in Table 1. SMs were younger (mean age, 56±13 years) and had milder baseline stroke severity (median admission NIHSS score, 4 points; interquartile range, 4 to 8) compared with patients with confirmed AIS (mean age, 67±14 years; median admission NIHSS score, 8 points; interquartile range, 4 to 14; $P<0.001$). Atrial fibrillation was less prevalent in SMs (11% versus 30%; $P=0.002$), whereas

pretreatment systolic blood pressure and glucose levels were higher ($P<0.01$) in patients with confirmed AIS.

IVT was not complicated with sICH (0%; 95% CI, 0% to 5.5%) or orolingual edema (0%; 95% CI, 0% to 5.5%) in SM. A total of 96% (54 of 56) of SMs were functionally independent at hospital discharge. The length of hospitalization was shorter and neurological improvement was greater in SM compared with confirmed AIS ($P<0.001$; Table 1).

Discussion

To the best of our knowledge, there are only 4 studies evaluating the prevalence and outcomes of SM among consecutive initially diagnosed AIS treated with IVT (Tables 2 and 3).^{2,4–6} The prevalence of SM in our cohort (10.4%) is comparable to the findings of these reports (3% to 13%). After pooling our findings with the data from these registries (collective sample of 147 SM treated with intrave-

Table 3. Prevalence and Outcomes of SM Among Patients Treated With IVT Across Different Stroke Registries

Registry	IVT (No.)	SM (No., %)	sICH in SM (No., %)	OE in SM (No., %)	FI in SM (No., %)
Michigan ⁴	151	6 (4%)	0	NA	1 (17%)†
Basel ⁵	250	7 (3%)	0	0	6 (86%)‡
Houston ⁶	512	69 (13%)	0	0	60 (87%)†
Pittsburgh ²	254	9 (4%)	NA	NA	NA
Phoenix	539	56 (10%)	0	0	54 (96%)†
Overall	1706	147 (9%)	0 (0%)	0 (0%)	121 (88%)
		(95% CI, 7% to 10%)	(95% CI,* 0% to 2.3%)	(95% CI,* 0% to 2.4%)	(95% CI,* 81% to 93%)

SM indicates stroke mimic; IVT, intravenous thrombolysis; sICH, symptomatic intracranial hemorrhage; OE, orolingual edema; FI, functional independence defined as a modified Rankin Scale score of 0 to 1; NA, not available.

*Calculated by the Adjusted Wald method.

†At hospital discharge.

‡At 3 mo.

nous tPA), the rates of sICH and orolingual edema are 0% (0 of 138 and 0 of 132, respectively), with the corresponding upper 95% CIs reaching 2.3% and 2.4%, respectively (Table 3). Our findings are also consistent with 2 of the previous studies documenting excellent functional outcomes in SMs treated with IVT (nearly 90% functional independence at hospital discharge⁶ or at 3 months⁵). Interestingly, the similar findings between our and previous registries may be related to the homogeneity and relatively uniform definition of SM across all studies (Table 2) that were conducted at comprehensive tertiary care stroke centers in North America (n=4) and in Europe (n=1) with expertise in intravenous tPA administration according to international (American Heart Association and European Stroke Organization) recommendations. Alternatively, favorable outcomes may be attributed to the underlying etiology in SM, including conversion disorder, migraine, or seizure in the vast majority of cases both in our and previous reports (Table 2).^{2,4–6} Another plausible explanation for the high rates of functional independence in SMs treated with IVT may be related to the lower admission NIHSS scores documented both in our and previous (Houston and Basel)^{5,6} series.

Caveats exist in the implications of this body of work. First, negative publication bias may have deterred other physicians from sharing their experiences regarding potential pitfalls of tPA administration in situations in which incorrect patient selection resulted in complications, especially serious ones. Second, brain MRI with diffusion-weighted imaging sequences has limitations in sensitivity related to brain stem location, infarct size (lacunar infarction), and the earliest times from onset. Thus, it cannot be excluded that some cases with brain ischemia may have been missed on follow-up neuroimaging studies and consequently have incorrectly been classified as SM.

In conclusion, the present pooled analysis (including homogeneous series of patients with common demographic characteristics from different tertiary care stroke centers across Europe and North America) indicates that IVT does not adversely affect the favorable natural history of SM, and treatment benefit from tPA would not be counterbalanced by the potential for harm to patients presenting with conditions mimicking AIS (a common concern among emergency physicians for precluding tPA use).^{9,10} Although a higher tPA dose is used for acute myocardial infarction (1.1 mg/kg instead of 0.9 mg/kg for AIS), the sICH rate in these patients is approximately 0.5%.¹¹ This is lower than the upper 95% CI of sICH rate documented in our pooled analysis (2.3%). On the other hand, the differential diagnosis of SM from acute cerebral ischemia often requires a time-consuming diagnostic work-up that may result in lengthening the onset-to-treatment time or even denying IVT in certain eligible candidates. Given that the efficacy of IVT is related to the faster tPA delivery,¹² and after taking into account the excellent functional outcome reported in SM treated with IVT (with almost

9 of 10 patients achieving functional independence within 3 months), our pooled analysis offers reassurance to stroke clinicians not to preclude potential candidates for thrombolytic therapy based on the sole concern that their neurological symptoms may be attributed to SM.

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