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Safety of Protocol Violations in Acute Stroke tPA Administration

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Abstract

Background—Intravenous (IV) tissue plasminogen activator remains the only approved therapy for acute ischemic stroke (AIS) in the United States; however, less than 10% of patients receive treatment. This is partially because of the large number of contraindications, narrow treatment window, and physician reluctance to deviate from these criteria.

Methods—We retrospectively analyzed consecutive patients who received IV thrombolysis at our stroke center for National Institute of Neurological Disorders and Stroke (NINDS) protocol violations and rates of symptomatic intracerebral hemorrhage (sICH). Other outcome variables included systemic hemorrhage, modified Rankin Scale at discharge, and discharge disposition.

Results—A total of 212 patients were identified in our stroke registry between 2009 and 2011 and included in the analysis. Protocol violations occurred in 76 patients (36%). The most common violations were thrombolysis beyond 3 hours (26%), aggressive blood pressure management (15%), elevated prothrombin time (PT) or partial thromboplastin time (PTT) (6.6%), minor or resolving deficits (4.2%), unclear time of onset (3.9%), and stroke within 3 months (3%). There were no significant differences in any of the safety outcomes or discharge disposition between patients with or without protocol violations. Controlling for age, National Institutes of Health

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Stroke Scale on admission, and glucose on admission, there was no significant increase in sICH (odds ratio: 3.8; 95% confidence interval: .37–38.72) in the patients who had protocol violations.

Conclusions—Despite more than one third of patients receiving thrombolysis with protocol violations, overall rates of hemorrhage remained low and did not differ from those who did not have violations. Our data support the need to expand access to thrombolysis in AIS patients.

Keywords

Acute ischemic stroke; thrombolysis; patient safety; protocol violation; symptomatic intracerebral hemorrhage

Introduction

Stroke is the fourth leading cause of death and a major cause of disability in the United States.¹ Intravenous (IV) tissue plasminogen activator (tPA) remains the only approved therapy for these patients²; however, in the United States, the Food and Drug Administration (FDA) indication is only for use within 3 hours of symptom onset. Currently, less than 10% of patients receive this therapy.^{3,4} The cause for this is likely multifactorial.⁵ Williams et al⁶ have proposed that this may be because of poor public awareness of stroke symptoms and available treatment options. Additional factors that contribute to the low utilization of tPA may be the large number of contraindications from the NINDS protocol, on the drug label or individual hospital policy. Many physicians may be reluctant to deviate from these criteria for fear of an increased risk of symptomatic intracerebral hemorrhage (sICH) and potential litigation.⁷

Interestingly, several criteria used for tPA exclusion are not based on strong clinical data. Internationally, evidence is starting to accumulate that many of these criteria may be too strict and that tPA can be safely delivered in patients previously thought ineligible.^{8–12} Leading stroke centers are expanding their thrombolysis protocols beyond the criteria proposed from early clinical trials. Given the limitations on tPA access imposed by these criteria, particularly the 3-hour time window restriction, we sought to determine the safety of thrombolysis in the US “Stroke Belt” patients who had defined contraindications to tPA administration.

Methods

Study Population

Consecutive patients presenting to our tertiary academic center from January 2009 to December 2011 were queried from the prospectively collected University of Alabama at Birmingham stroke registry database. To ensure complete capture of all patients admitted with ischemic stroke, the charts were identified of all patients (1) discharged from our facility with the *International Classification of Diseases, Ninth Revision (ICD-9)*, codes 433, 434, and 436 and (2) treated with t-PA according to pharmacy records. The electronic medical record of patients identified by any of these approaches was retrospectively reviewed by one of the authors (R.B.S.) to confirm the diagnosis of acute ischemic stroke (AIS) and tPA administration. Baseline demographics, stroke severity (as measured by the

National Institutes of Health Stroke Scale [NIHSS] score), and acute treatment recorded in the stroke registry were verified on all patients with a confirmed diagnosis of AIS. Medical records were then retrospectively reviewed to collect additional information on medical history, medication use, imaging data, laboratory results, and outcomes. Special attention was paid to the presence of contraindications or label warnings to IV t-PA. Patients undergoing thrombolysis at outside facilities before transfer (drip and ship) were excluded from the analysis because of incomplete data.

Definition of Contraindications

We defined a tPA protocol violation as any contraindication listed in the original NINDS tPA stroke study.² Although newer guidelines have refined some of the criteria,⁷ they are not used at all hospitals and many centers may use protocols derived from the original NINDS trial. For the purposes of this study, we considered treatment beyond the FDA-approved 3-hour time window as a protocol violation as our experience indicates that most hospitals in our treatment area still adhere to the time window from the NINDS trial.² Aggressive blood pressure control was defined as the need for continuous infusion of an IV antihypertensive to lower blood pressure to an acceptable range.² Although not an exclusion criterion from the NINDS trial, we also examined patients aged 80 years or older as some providers may view this as a contraindication based on evidence that these patients may have poorer outcomes.¹³

Outcomes

Our primary outcome was sICH, defined as a space-occupying hemorrhage (PH1 or PH2) not seen on previous imaging coupled with 4 points or more neurologic deterioration on the NIHSS.¹⁴ Other outcomes assessed included any hemorrhagic transformation (HT, as determined by computed tomography or magnetic resonance imaging), systemic hemorrhage, unfavorable short-term functional outcome (as measured by modified Rankin scale [mRS] score 3–6 at discharge), and unfavorable disposition (discharged to a location other than home or in-patient rehabilitation).

Statistical Analysis

Baseline characteristics were evaluated using chi-square and *t* tests. Logistic regression models were used to assess the relationship between a tPA protocol violation and outcomes. Models were adjusted for age, NIHSS on admission, and glucose on admission. As this was an exploratory analysis, no adjustments were made for multiple comparisons.¹⁵ All tests were performed at the alpha .05 level. The University of Alabama at Birmingham Institutional Review Board approved this study.

Results

During the 36-month period, a total of 308 patients were identified as AIS patients treated with tPA. We excluded 96 patients as they had received tPA at an outside facility before transfer, leaving 212 patients for analysis. The baseline demographics of these patients are detailed in Table 1.

Protocol violations occurred in 76 patients (36%). Table 2 describes the frequency of each violation. The most common violations were aggressive blood pressure management, elevated PT/PTT, minor or resolving deficits, unclear time of onset, and stroke within 3 months. In patients requiring aggressive blood pressure lowering, nicardipine hydrochloride was most frequently used although 4 patients were treated with IV nitroprusside. The tPA bolus was held until blood pressure had been successfully reduced to below 185/110 mm Hg. Interestingly, 3 patients (1.4%) treated with tPA had a history of ICH, although this information may not have been available at the time the treatment decision was made.

The rates of sICH (4% versus 1.5%, $P = .350$), HT (16% versus 15%, $P = .915$), and systemic hemorrhage (5% versus 4%, $P = .725$) were nearly identical in patients with tPA protocol violations when compared with patients without violations (Table 3). Even after controlling for age and NIHSS and glucose on admission, the presence of a t-PA protocol violation was not associated with a significant increase in the odds of sICH (odds ratio [OR]: 3.80; 95% confidence interval [CI]: .37–38.72) or an increase in the odds of any HT (OR: 1.02; 95% CI: .45–2.30, Table 4). In univariable analysis, age of 80 years or older was not a significant independent predictor of sICH (OR: .52; 95% CI: .41–6.64) or HT (OR: .87; 95% CI: .37–2.02). Lastly, an unfavorable mRS at discharge (71% versus 58%, $P = .074$) and unfavorable discharge disposition (39% versus 28%, $P = .134$) were not significantly different in patients with violations and patients without violations. After adjusting for age and NIHSS and glucose on admission, an association was detected between an unfavorable discharge mRS and patients who received tPA with protocol violations (OR: 2.00; 95% CI: 1.03–3.89). The association between protocol violations and discharge mRS is no longer statistically significant when this model is also adjusted for tPA treatment between 3 and 4.5 hours (OR: 1.90; 95% CI: .94–3.81).

Discussion

Our data suggest that tPA administration in patients with selected label or protocol contraindications may be safe and does not significantly increase the risk of sICH. Furthermore, short-term outcomes are not significantly affected. Despite physicians frequently citing label and protocol contraindications as reasons to withhold tPA, there has been little data about the safety of IV thrombolysis in these patients. Recently, data have started to emerge from Europe, supporting the use of tPA in patients with contraindications.^{10,11} Our study examines the safety of “off-label” tPA use based on protocols commonly used in the United States. Despite more than one third of patients receiving tPA in violation of the NINDS protocol, overall rates of hemorrhage remained low in patients with violations. Although the percentage of patients who developed sICH was higher in the violation group, this did not reach statistical significance.

At our center, the most common violation was treatment beyond the 3-hour time window. The European Cooperative Acute Stroke Study-3 (ECASS-3) trial¹⁶ has demonstrated that tPA can be effectively delivered to patients between 3 and 4.5 hours from symptom onset although a significantly higher rate of sICH was reported in patients treated in this extended window. Although the Safe Implementation of Treatments in Stroke (SITS) registry did not find this same association with sICH,¹⁷ treatment beyond 3 hours may still have contributed

to the higher percentage of our patients with sICH. Physicians should be mindful of the potential for increased sICH in patients treated beyond 3 hours and should weigh this against the potential benefits as described in the ECASS-3 trial. Aggressive blood pressure control, generally with a continuous infusion of nicardipine hydrochloride, was also a frequent violation. It should be noted that these patients had their blood pressure reduced to below 185/110 mm Hg before tPA administration. This has also previously been demonstrated to be safe.¹⁸ Our study demonstrates that collectively these violations do not significantly increase adverse outcomes.

We also assessed if these protocol violations affected the patient's functional outcome on discharge or their discharge disposition. Prior studies reported that patients receiving tPA within 3 hours of symptom onset are more likely to be discharged home; however, little is known about discharge disposition in patients who were treated off label.¹⁹ In our study, a higher percentage of patients with protocol violations had an unfavorable discharge disposition; however, this was not statistically different from patients without protocol violations. After adjusting for age and NIHSS and glucose on admission, we did observe an association between patients with protocol violations and poor short-term functional outcome. When we further adjusted for treatment between 3 and 4.5 hours, this association was no longer significant indicating that the poor functional outcomes we observed were driven by tPA treatment during the extended time window. Overall, although our study suggests that functional outcomes may be slightly worse in patients with protocol violations, we found no difference in discharge disposition.

At our center, we do not use an upper age limit for tPA delivery and it is generally not considered a protocol violation at most US hospitals. Several studies have shown that tPA can be safely administered to older patients, even in extended time windows.^{20–23} In our study population, we did not find an increased risk of sICH or HT in patients 80 years or older. This reinforces the existing data that tPA should not be withheld solely based on patient age.

Recently, the Safe Implementation of Treatments in Stroke-East Registry (SITS-EAST) described their experience with off-label tPA use based on the European license.²⁴ Similar to our study population, the most common label violations were treatment beyond 3 hours (13.1%) and use of IV antihypertensives (8.3%). Overall, they reported that 34.3% of their patients had label violations. Despite this being a similar percentage compared with our center, they found that their patients had a significantly higher rate of symptomatic hemorrhage (although this difference was not seen in the multivariable analysis). Furthermore, they found that patients treated off label had worse outcome at 3 months. Our results differ from this and may be explained by differences in European exclusions from the FDA label.

The limitations of our study warrant discussion. First, it is limited by its retrospective nature. This cross-sectional study employed a combination of both retrospective and prospective data collection. It is possible that a purely prospective approach could have yielded more precise data with additional data points. Second, our study population is one that is served at a single tertiary care center in the US Stroke Belt with a higher tPA utilization rate than

community hospitals. Although our sample may generalize well to the Stroke Belt, it may not generalize equally well to other populations. Third, our study includes only short-term outcomes; however, disability status at discharge has been shown to be predictive of the 90-day functional outcome.²⁵ Fourth, our study only investigated deviations from the NINDS protocol. Although this serves as the basis for many hospital tPA protocols, it may not represent policies at all hospitals. Furthermore, we analyzed contraindications as a whole and each contraindication does not carry the same risk of adverse outcome. Finally, our sample size may limit our ability to detect existing differences between groups. Despite these limitations, our study is unique in that it is one of the few studies to examine tPA protocol deviations for acute stroke in a US population and we hope that it will encourage further investigation of protocol violations and tPA safety at a larger level.

In summary, our study provides data to support the use of tPA in spite of many of the listed protocol contraindications. Safety outcomes and discharge disposition do not differ significantly from patients treated according to protocol. Physicians should weigh the risks and benefits of treating patients “off protocol,” but our data suggest that tPA can be safely administered in many of these patients. These findings agree with the European literature and support the need to expand access to IV tPA in the United States.

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Table 1

Demographics and baseline characteristics of patients treated with tPA

Variable	Treated with IV t-PA (N = 212)
Gender	
Male	55% (116)
Age, median (range)	68 (24–99), IQR 55, 82
Race	
White	61% (129)
Black	38% (80)
Asian/Pacific Islander	1% (3)
Ethnicity	
Hispanic	0% (0)
Medical history	
Diabetes	26% (55)
Hypertension	76% (162)
Dyslipidemia	32% (69)
Atrial fibrillation	20% (42)
Congestive heart failure	13% (27)
Medications	
Oral diabetes medications	16% (33)
Antihypertensives	62% (132)
Antiplatelet agents	38% (80)
Warfarin	5% (11)
Laboratory values, median (range)	
Glucose	116 (17–536), IQR 101, 143
INR	1.07 (.83–2.37), IQR 1.02, 1.14
PTT	28 (15–69), IQR 26, 30
Current smoker	28% (60)
Admission NIHSS, median (range)	8 (0–32), IQR 5, 14
Intra-arterial treatment used	2% (5)

Abbreviations: INR, international normalized ratio; IQR, inter-quartile region; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Table 2

Frequency of protocol violations of patients treated with IV tPA

Violation type	Percentage with violations (total treated, N = 212)
>3 h or unclear time of onset	26 (56/212)
Aggressive blood pressure control required	17 (36/212)
Elevated PT/PTT	6.6 (14/212)
Minor/resolving symptoms	4.2 (9/212)
Stroke within 3 mo	3 (6/212)
Diastolic blood pressure >110 mm Hg	1.9 (4/212)
Platelets < 100,000/ μ L	1.9 (4/212)
Systolic blood pressure >185 mm Hg	1.4 (3/212)
History of intracerebral or subarachnoid hemorrhage	1.4 (3/212)
Seizure at onset	1.4 (3/212)
Glucose <50 or >400 at time of bolus	.9 (2/212)
Major surgery within 14 d	.5 (1/212)
Gastrointestinal or genitourinary hemorrhage	.5 (1/212)
Arterial puncture within 7 d	0 (0/212)
Symptoms resembling subarachnoid hemorrhage	0 (0/212)
Traumatic brain injury within 3 mo	0 (0/212)

Abbreviations: IV, intravenous; PT, prothrombin time; PTT, partial thromboplastin time; tPA, tissue plasminogen activator.

Table 3

Outcomes in patients with protocol violations

Outcome variable	No violation	Violation	<i>P</i> value
Symptomatic ICH	1.5% (2/136)	4% (3/75)	.350
Hemorrhagic transformation	15.4% (21/136)	16% (12/75)	.915
Systemic hemorrhage	3.7% (5/136)	5.3% (4/76)	.725
mRS score 3–6 at discharge	58.2% (78/134)	70.7% (53/75)	.074
Not discharged to home or inpatient rehabilitation	28.2% (37/131)	38.6% (27/70)	.134

Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin Scale.

Table 4

Odds of outcomes of interest in patients with protocol violations as compared with patients without protocol violations

Outcome variable	Crude OR (95% CI)	Adjusted* OR (95% CI)
Symptomatic ICH	2.79 (.46–17.09)	3.80 (.37–38.72)
Any hemorrhagic transformation	1.04 (.48–2.26)	1.02 (.45–2.30)
Systemic hemorrhage	1.46 (.38–5.59)	1.37 (.35–5.36)
mRS score 3–6 at discharge	1.73 (.95–3.16)	2.00 (1.03–3.89)
Not discharged to home or inpatient rehabilitation	1.59 (.86–2.95)	1.56 (.79–3.08)

Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

* Adjusted for age and NIHSS and glucose on admission.