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Protocol deviations before and after IV tPA in community hospitals

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Abstract

Background—Protocol deviations before and after tPA treatment for ischemic stroke are common. It is unclear if patient or hospital factors predict protocol deviations. We examined predictors of protocol deviations and the effects of protocol violations on symptomatic intracerebral hemorrhage.

Methods—We used data from the INSTINCT trial, a cluster-randomized, controlled trial evaluating the efficacy of a barrier assessment and educational intervention to increase appropriate tPA use in 24 Michigan community hospitals, to review tPA treatments between 2007 and 2010. Protocol violations were defined as deviations from the standard tPA protocol, both before and after treatment. Multi-level logistic regression models were fitted to determine if patient and hospital variables were associated with pre-treatment or post-treatment protocol deviations.

Results—During the study, 557 patients (mean age 70; 52% male; median NIHSS 12) were treated with tPA. Protocol deviations occurred in 233 (42%) patients: 16% had pre-treatment deviations, 35% had post-treatment deviations, and 9% had both. The most common protocol deviations included elevated post-treatment blood pressure, antithrombotic agent use within 24 hours of treatment, and elevated pre-treatment blood pressure. Protocol deviations were not associated with symptomatic intracerebral hemorrhage, stroke severity, or hospital factors. Older age was associated with pre-treatment protocol deviations (adjusted OR 0.52; 95% confidence interval 0.30-0.92). Pre-treatment deviations were associated with post-treatment deviations (adjusted OR 3.20; 95% confidence interval 1.91-5.35).

Conclusions—Protocol deviations were not associated with symptomatic intracerebral hemorrhage. Aside from age, patient and hospital factors were not associated with protocol deviations.

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Keywords

stroke; thrombolysis; Emergency Department; tPA

Introduction

Protocols for the administration of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke have been adapted from the NINDS tPA trial[1] and are recommended by guidelines.[2] Previous studies have shown that protocol deviations before and immediately after tPA are common,[3-16] however, the clinical implications of these deviations are uncertain. Some studies have found that protocol deviations are associated with symptomatic intracerebral hemorrhage (sICH) and poor outcome[3, 9-13], while other reports have not found this association.[4-8, 15-19] Because poor outcomes have been associated with protocol deviations, identifying predictors of these deviations may be useful to improve the quality of acute stroke care. Predictors of protocol deviations are not well understood. Most prior studies examining protocol deviations evaluated small number of patients, were retrospective reviews of a single center's experience, or both. Using prospectively collected data from the INSTINCT (INcreasing Stroke Treatment through INterventional behavior Change Tactics) trial[20] we aimed to: 1) determine if patient or hospital factors were associated with protocol deviations and 2) examine the effects of protocol deviations before or immediately after tPA on sICH.

Methods

The INSTINCT trial was a multi-center, cluster-randomized, controlled trial evaluating the efficacy of a barrier assessment and educational intervention to increase appropriate tPA use in Emergency Departments in Michigan community hospitals. The methods and results of the INSTINCT trial have been described previously.[20] Briefly, community hospitals in Michigan's Lower Peninsula were randomly selected and matched with a geographically separated partner hospital with ± 20% of the index hospital's annual stroke admissions. This process was repeated for a total of 12 hospital dyads. One hospital in each pair received the INSTINCT intervention, the other hospital served as a control. Complete data on the physician cohort staffing the INSTINCT emergency departments has previously been reported.[21] In brief, 80% of the physician cohort completed emergency medicine residencies and 85% were board certified in emergency medicine. No significant inter-hospital differences in staff were identified. INSTINCT had complete capture of tPA use for ischemic stroke between 2007 and 2010.

This study was a *post-hoc* secondary analysis of the final INSTINCT dataset. All clinical information from the chart was abstracted using a previously described instrument with a high inter-rater reliability (kappa=0.74).[22] The chart abstracters were not aware of this analysis at the time the data was collected.

Protocol deviations were defined as deviations from the recommendations outlined in the American Heart Association guidelines at the time the trial was conducted.[23] All hospitals used guideline concordant protocols to treat patients with tPA. As the ECASS III study[24]

was published during the INSTINCT trial, protocol deviations for time to treatment were defined as treatment with IV tPA at more than 4.5 hours for patients who met ECASS III criteria, and treatment at more than 3 hours for others. Current guidelines support the expanded treatment window.[2] Pre-treatment blood pressure deviations were defined as treating a patient with IV tPA despite a blood pressure of greater than 185/110 (defined as the last documented pre-treatment blood pressure prior to tPA administration). Post-tPA hypertension was defined as two consecutive blood pressure readings, at least 30 minutes apart, greater than 180 mm Hg systolic or 105 mm Hg diastolic within the first 24 hours of tPA treatment. Patients were classified as having pre-treatment deviations, post-treatment deviations, or both. In contrast to the primary INSTINCT analysis[20], we used nursing reviewer assessment of protocol deviations, rather than physician ascertainment. This allowed for an evaluation of an extended set of variables that were not assessed by physician reviewers.

Study Covariates

Covariates were chosen based on *a priori* beliefs regarding which clinical and hospital factors would be associated with protocol deviations. Medical co-morbidities, antiplatelet use, and neurologic consultation were obtained from the medical record. Hypertension, diabetes, hyperlipidemia, and anti-platelet use were defined as a history of these conditions documented in the medical record or if the patient was taking medications to treat these conditions. sICH was defined as radiographic ICH with associated clinical worsening based on a retrospective review of the hospital chart (NINDS tPA trial definition[1]). Inpatient mortality and modified Rankin Scale (mRS) at discharge were abstracted based on previously described methods.[14] Hospital size and Joint Commission Primary Stroke Center (JC PSC) certification were self-reported by the participating hospitals. Five hospitals were JC PSC certified prior to the INSTINCT trial and 3 hospitals obtained JC PSC certification during the trial. None of the hospitals had other forms of stroke certification. The University of Michigan and local institutional review boards approved the INSTINCT trial.

Statistical analysis

Descriptive statistics were computed for demographic and clinical characteristics. Patient and hospital characteristics and the presence of protocol deviations were compared using chi-squared tests for categorical variables and *t* tests for continuous variables. Multi-level logistic regression models were fitted to determine whether patient and hospital variables were associated with pre-treatment protocol deviations or post-treatment protocol deviations. The models included the following patient level covariates: age, NIHSS, gender, history of hypertension, current anti-platelet therapy, stroke onset to ED arrival time. For analysis, age, symptom onset to ED arrival interval, and NIHSS were classified into tertiles. Hospital level covariates included: INSTINCT intervention group assignment (versus control), hospital size, and JC PSC certification. Hospitals that obtained JC PSC certification during the INSTINCT trial were analyzed as having JC PSC certification. Pre-treatment protocol deviation was included as a covariate in the model for post-treatment deviation. A random effects logistic regression model was used to account for differences in protocol deviations at individual hospitals. Analysis was performed using SAS version 9.1.3.

Results

All 557 patients treated with tPA in the INSTINCT trial were included in the analysis. Six patients had missing data for post-treatment blood pressure control and we assumed that these patients did not have a post-treatment blood pressure deviation. Pre-treatment protocol deviations were present in 90 (16%) patients. Post-treatment protocol deviations were present in 195 (35%) patients. Forty-two percent (n=233) of patients had at least one protocol deviation (Table 1). In univariate analyses: older age, white race, prior stroke, history of hypertension, and antiplatelet therapy were significantly associated with a deviation from the standard protocol. There was no association between NIHSS, neurologic consultation, hospital size, or JC PSC certification and protocol deviations.

There were 103 pre-treatment deviations in 90 patients and 217 post-treatment deviations in 195 patients (Table 2). Treatment with tPA despite elevated blood pressure was the most common pre-treatment deviation and occurred in 39 patients (38% of pre-treatment deviations). Twenty-nine patients were treated outside the recommended time window. The most common post-treatment protocol deviation was failure to control hypertension, identified in 125 patients (58% of post-treatment deviations). Individual hospital deviations ranged from 17% to 67% of tPA treatments (additional details are in the online supplement).

In the fully adjusted models (Table 3), only older age was significantly associated with pre-treatment protocol deviations (adjusted odds ratio [OR] 0.52; 95% confidence interval [CI] 0.30-0.92). When post-treatment protocol deviations were evaluated with adjustment for pre-treatment protocol deviations, age was not associated with either pre- or post-tPA treatment protocol deviations; however, pre-treatment protocol deviations were associated with post-treatment protocol deviations (adjusted OR 3.20; 95% CI 1.91-5.35). Symptom onset to arrival time, stroke severity, hypertension, and antiplatelet use did not predict protocol deviations. The INSTINCT intervention and JC PSC certification were not associated with a reduction in protocol deviations.

Thirty eight of the 557 study patients (6.8%) had a sICH. Protocol deviations did not predict sICH, as 17 (7.3%) of patients with any protocol deviation and 21 (6.5%) of patients without a protocol deviation had a sICH (P=0.71). Inpatient mortality and functional outcome were not associated with having a protocol deviation.

Discussion

Protocol deviations were common in stroke patients treated with tPA in Michigan community hospitals from 2007-2010. Protocol deviations were not associated with sICH, inpatient mortality or functional outcome at hospital discharge. Post-treatment deviations constituted the majority of deviations. The most frequent protocol deviations included treatment despite elevated blood pressure, treatment outside recommended time windows, failure to control hypertension, and use of antithrombotic agents within 24 hours of tPA. Symptom onset to arrival time was not associated with protocol deviations. Older age was associated with pre-treatment protocol deviations and pre-treatment protocol deviations were associated with post-treatment protocol deviations.

Data suggests that some patients at risk for stroke would prefer death to living with severe disability.[25] This may lead physicians to treat older patients because of a concerns that stroke related disability may be worse than the potential adverse effects of tPA administered outside standard protocols. It is unclear why pre-treatment deviations predicted post-treatment deviations. Failure to control hypertension was a common deviation, and since pre-treatment and post-treatment hypertension are not independent, hypertension may explain the association between pre-treatment and post-treatment deviations.

Studies have questioned the need for certain aspects of standard protocols[26-28] and commentators have recognized the need to critically examine tPA exclusion criteria that decrease the number of patients eligible for treatment.[29] While this work should be encouraged, it should be noted that certain parts of the protocol likely have a stronger relationship to outcomes than others. Treating a patient with a two month old myocardial infarction is likely safer[26] than administration of aspirin early after tPA.[30] This nuance is reflected in the current guidelines[2] and a recent revision to the IV tPA (alteplase) package insert has removed some specific examples of contraindications to treatment.[31] While each aspect of the standard thrombolysis protocol may not be supported by strong evidence from clinical trials, compliance with the protocol should maximize the likelihood that populations of patients will achieve a similar treatment effect as measured in the randomized controlled trials.

There are a number of barriers that prevent clinicians from following protocols outlined in guidelines.[32] Quality improvement programs have been shown to decrease the rate of protocol deviations in acute stroke treatment, even in the setting of increased tPA use.[6, 33] However, since there was no association between the INSTINCT intervention or JC PSC certification and reduced protocol deviations in our study, there is likely substantial variability in the effectiveness of these quality improvement programs.

Our study has a number of limitations. As this was a *post-hoc* analysis our conclusions should be considered hypothesis generating and prompt further research. The hospitals that participated in the INSTINCT trial may not be representative of community hospitals at large. We did not collect data on emergency department length of stay or DNR status, which may be related to protocol deviations. While we did not find an association between protocol deviations and INSTINCT intervention status, sICH, inpatient mortality, or JC PSC certification status, this study was not designed, nor powered, to evaluate these endpoints so this data should be considered exploratory. Our study examined a composite measure of protocol deviations and was not powered to evaluate particular, specific deviations. Some deviations may have more clinical importance than others, for instance, the magnitude and duration of a hypertension deviation is important, but we did not capture this level of detail. The lack of clinical context surrounding the protocol deviations also tempers our results, however, given the high frequency of protocol deviations, clinical necessity is unlikely to account for more than a small number of deviations. In addition, some of the most common deviations may be an artifact of documentation practices. For example, a patient could have an appropriate blood pressure at the time of treatment; however this reading may not get transcribed from the monitor into the medical record. We may also have missed deviations that occurred, but were not documented in the chart. Our analysis does not reflect stroke

volume[34, 35] or quality measures such as dysphagia screening[36] that may be associated with improved outcomes. An additional limitation is the lack of longer-term outcome data in INSTINCT. While we have information on sICH, inpatient mortality, and functional outcome at discharge, we do not have data for outcomes after hospital discharge. Strengths of our study include the large number of patients and its community hospital population that reflects where the majority of stroke patients in the US are treated. When comparing our study to prior work, protocol deviations have been defined differently in different studies which limit direct comparisons.

In summary, protocol deviations during and after tPA treatment are common, but in this study, were not associated with sICH, in-patient mortality, or functional outcome at hospital discharge. This analysis indicates community hospitals can safely treat stroke patients with IV tPA, though future work should investigate the reasons protocol deviations occur and develop interventions targeted toward improving adherence to guideline recommended care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient characteristics

	No protocol deviations (n=324)		Protocol deviations (n=233)		P value
	Mean or number	**Percent or SD**	**Mean or number**	**Percent or SD**	
Age	68.6	14.94	71.7	14.81	**0.02***
Male	172	53.1%	118	50.6%	0.57
Race					**0.05***
White (non-Hispanic)	238	73%	187	80%	
Black	26	8%	19	8%	
Hispanic	11	3%	1	0.4%	
Unknown	49	15%	26	11%	
Onset to arrival time (minutes)	81.3	8.3	92.4	9.6	0.38
NIHSS	12.0	5.7	12.00	5.8	0.96
Prior stroke	51	15.7%	52	22.3%	**0.05***
Prior TIA	34	10.5%	34	14.6%	0.15
History of diabetes	73	22.5%	60	25.8%	0.38
History of hypertension	229	70.7%	187	80.3%	**0.01***
History of hyperlipidemia	157	48.5%	127	54.5%	0.16
Coronary artery disease	94	29.0%	81	34.8%	0.15
CHF	38	11.7%	34	14.6%	0.32
Atrial fibrillation	62	19.1%	60	25.8%	0.06
Valvular heart disease	23	7.1%	12	5.2%	0.35

	No protocol deviations (n=324)		Protocol deviations (n=233)		P value
	Mean or number	**Percent or SD**	**Mean or number**	**Percent or SD**	
Smoker	83	25.6%	48	20.6%	0.17
Antiplatelet therapy	146	45.1%	125	53.7%	**0.05***
mRS at discharge					0.30
0	33	10.2%	17	7.3%	
1	26	8.0%	24	10.3%	
2	40	12.4%	20	8.6%	
3	46	14.2%	27	11.6%	
4	83	25.6%	58	24.9%	
5	61	18.8%	58	24.9%	
6	35	10.8%	29	12.5%	
sICH	21	6.5%	17	7.3%	0.71
Inpatient mortality	35	10.8%	29	12.5%	0.55
JC PSC	115	47.8%	113	49.8%	0.65
INSTINCT intervention at hospital	136	42.0%	99	42.5%	0.90
Hospital size					0.61
≤ 150 beds	45	13.9%	39	16.7%	
151-250 beds	111	34.3%	80	34.3%	
≥ 251 beds	168	51.9%	114	48.9%	
Consultation with neurology					0.67
In person	172	53.1%	116	49.8%	
By phone	128	39.5%	96	41.2%	
No consult	24^	7.4%	21	9.0%	

*p<0.05

^includes 2 cases with missing data

Table 2

Pre- and post-tPA treatment protocol deviations

Deviation	n, (%)
Pre-tPA treatment	
Elevated BP at time of treatment*	39 (38%)
Treatment >3 (or 4.5†) hours after last normal time	29 (28%)
Stroke within 3 months	8 (8%)
Minor symptoms	6 (6%)
Spontaneously clearing symptoms	4 (4%)
Myocardial infarction within 3 months	3 (3%)
Active bleeding or trauma	3 (3%)
Thrombocytopenia (platelet count <100,000 mm^3)	3 (3%)
Seizure at symptom onset	3 (3%)
GI or GU hemorrhage within 3 weeks	2 (2%)
Major surgery within 14 days	1 (1%)
Head trauma within 3 months	1 (1%)
Not stroke	1 (1%)
Total	103 deviations in 90 patients
Post-tPA treatment	
Hypertension‡	125 (58%)
Antiplatelet use within 24 hours	61 (28%)
Anti-coagulant use within 24 hours	31 (14%)
Total	217 deviations in 195 patients

*Defined as the last documented pre-treatment blood pressure prior to tPA administration >185/110.

†For patients who met ECASS III criteria.

‡Defined as two consecutive blood pressure readings, at least 30 minutes apart, >180/105 within the first 24 hours of tPA treatment.

Table 3

Predictors of protocol deviations

	Predictors of pre-treatment protocol deviations	Predictors of post-treatment protocol deviations
	Adjusted OR (95% CI)	**Adjusted OR (95% CI)**
Patient factors		
Age		
<62	0.35 (0.18-0.68)	1.03 (0.62-1.71)
62 to 79	**0.52 (0.30-0.92)**	1.02 (0.64-1.62)
>79	Reference	Reference
Male	0.73 (0.44-1.22)	1.14 (0.76-1.70)
NIHSS		
1-7	1.58 (0.82-3.02)	0.81 (0.49-1.33)
8-14	1.43 (0.79-2.60)	0.96 (0.62-1.50)
≥15	Reference	Reference
Onset to arrival time		
<46 min	0.79 (0.44-1.42)	1.15 (0.72-1.83)
46-73 min	0.60 (0.33-1.08)	0.87 (0.55-1.39)
>73 min	Reference	Reference
History of hypertension	1.46 (0.75-2.84)	1.26 (0.77-2.04)
Antiplatelet use	0.82 (0.50-1.41)	1.17 (0.78-1.76)
Pre-treatment deviation	Not applicable	**3.20 (1.91-5.35)**
Hospital factors		
INSTINCT intervention	1.04 (0.56-1.95)	1.01 (0.64-1.61)
Hospital size		
≤150 beds	1.08 (0.45-2.56)	1.35 (0.72-2.54)
151-250 beds	0.87 (0.44-1.71)	1.06 (0.65-1.73)
≥251 beds	Reference	Reference
JC PSC Certified	1.31 (0.68-2.52)	1.08 (0.67-1.73)

JC PSC = Joint Commission Primary Stroke Center