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tPA Prescription and Administration Errors within a Regional Stroke System

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Abstract

Background—IV tPA utilization in acute ischemic stroke (AIS) requires weight-based dosing and a standardized infusion rate. In our regional network, we have tried to minimize tPA dosing errors. We describe the frequency and types of tPA administration errors made in our comprehensive stroke center (CSC) and at community hospitals (CHs) prior to transfer.

Methods—Using our stroke quality database, we extracted clinical and pharmacy information on all patients who received IV tPA from 2010–11 at the CSC or CH prior to transfer. All records were analyzed for the presence of inclusion/exclusion criteria deviations or tPA errors in prescription, reconstitution, dispensing, or administration, and analyzed for association with outcomes.

Results—We identified 131 AIS cases treated with IV tPA: 51% female; mean age 68; 32% treated at CSC, 68% at CH (including 26% by telestroke) from 22 CHs. tPA prescription and administration errors were present in 64% of all patients (41% CSC, 75% CH, $p < 0.001$), the most common being incorrect dosage for body weight (19% CSC, 55% CH, $p < 0.001$). Of the 27 overdoses, there were 3 deaths due to systemic hemorrhage or ICH. Nonetheless, outcomes (parenchymal hematoma, mortality, mRS) did not differ between CSC and CH patients nor between those with and without errors.

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Study data were collected and managed using REDCap electronic data capture tools hosted at University of Utah. 1 REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

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Conclusion—Despite focus on minimization of tPA administration errors in AIS patients, such errors were very common in our regional stroke system. Although an association between tPA errors and stroke outcomes was not demonstrated, quality assurance mechanisms are still necessary to reduce potentially dangerous, avoidable errors.

Keywords

tPA; thrombolysis; stroke; systems of care

INTRODUCTION

Systemic intravenous tissue plasminogen activator (tPA) remains the only US FDA-approved treatment for acute ischemic stroke (AIS). Administration of tPA in AIS requires patient-specific weight-based dosing of 0.9 mg/kg (not to exceed 90 mg total dose) infused over 60 minutes with 10% of the total dose administered as an initial intravenous (IV) bolus over 1 minute as based on the NINDS t-PA trial protocol.(1) The most devastating complication encountered during tPA therapy is bleeding.(2) It is thus important to have a systematic approach to tPA administration so that it is done accurately, reducing the possibility of error.

As part of our systems-based approach to AIS care, we attempt to minimize tPA dosing and administration errors. For example, we systematically weigh patients at our comprehensive stroke center (CSC) to accurately calculate tPA dose and pharmacy discards extra tPA prior to administration. When performing phone- and telestroke-based consults, we ask the same of our community hospitals (CHs). Additionally, all patients accepted to our comprehensive stroke center after tPA administration are met by a multi-disciplinary team that includes an ED or critical care pharmacist who checks the dosing accuracy of tPA. Through this system, we observed frequent tPA medication errors in patients presenting to our hospital after or during tPA infusion. This motivated us to systematically study the frequency, types, and effects of deviations to the standard tPA protocol among patients treated in our region and whether these errors have led to worse outcomes.

METHODS

The University of Utah has a prospective registry of stroke patients treated with IV tPA either at our CSC or at a CH prior to transfer to us (drip-and-ship). Using this database, we retrospectively studied consecutive patients treated with tPA for presumed AIS from 1/2010 to 12/2011. We excluded patients treated via telephone or telestroke consult who were not subsequently transferred to the CSC.

In-house treatment at the CSC is managed by the brain attack team including an ED nurse, ED physician, pharmacist, neurology resident and either a vascular neurology attending or neurocritical care intensivist. CH staff includes an ED physician and nurse; none have consulting neurologists available for acute stroke cases. Stroke consultation to the CH was provided by the CSC stroke attending via telephone or telestroke. At the CSC, a sling scale is used to obtain an accurate weight for each stroke patient. The tPA order and dosing is verified by the ED pharmacist from 0700-0100 or by the central pharmacy from 0100-0700

and mixed in the IV center. Both at the CSC and via telephone/telestroke to the CHs, the standard protocol for treating these patients during this period was based on criteria established by the 2007 American Heart Association guidelines.(3)

Clinical information, including demographics, medical history, modified Rankin Scale (mRS) at discharge and at follow-up (when available), and discharge location, were abstracted from each patient's chart. NIH Stroke Scale (NIHSS) was prospectively recorded (86%) or retrospectively extracted (14%) using a validated method.(4) Referring hospital and use of telemedicine or telephone consultation were recorded for all transferred patients. tPA mixing and delivery data were retrospectively collected from air transport records, nursing records, and pharmacy data. Three School of Pharmacy faculty pharmacists with extensive experience in preparing tPA reviewed the charts to determine the presence and nature of the administration errors and graded them using the University HealthSystem Consortium Patient Safety Net (UHC PSN) scale for medication errors.(5) The pharmacists used uniform definitions for tPA medication errors to provide consistency in record review. Per CSC stroke protocol, all patients receive follow-up neuroimaging (CT or MRI) approximately 24 hours after tPA treatment; these were read by board-certified neuroradiologists. For this study, two separate vascular neurologists determined presence of parenchymal hematoma (PH) as defined by ECASS criteria;(6) differences in ratings were adjudicated by discussion.

Inclusion/exclusion criteria deviations based on the 2007 American Heart Association guidelines(7) were recorded but not counted as errors. tPA administration to patients with low NIHSS were intentional violations of a relative exclusion criteria and thus were not counted as errors. Possible tPA errors included: prescription errors (wrong dose ordered by > 1mg, inaccurate body weight by > 1kg, an agent other than alteplase, prescription sent to wrong area, total dose exceeding 90mg, or prescription written on an incorrect patient); reconstitution error (incorrect diluents other than sterile water, incorrect volume); dispensing error (prolonged delivery to bedside > 15 minutes), or administering error (bolus administration > 2 minutes, IV bag malfunction, incompatible or malfunctioning IV pump, tPA wasted in tubing, IV site error, or infusion > 60 min). We had the *a priori* hypothesis that the following errors would lead to an increased risk of PH: overdose for CSC-measured body weight, total dose > 90mg, or infusion > 60 minutes. CH weight was imputed from the administered tPA dose when body weight was not documented in transfer records. We presumed that the weight obtained at arrival to the CSC was accurate as this was measured in a systematic way.

The patients were stratified based on whether they received tPA at the CSC or CH, whether or not an error had been made in the tPA prescription or administration, and the specific error type. We analyzed outcomes for all patients and then separately for just those with a final discharge diagnosis of AIS (i.e., excluding stroke mimics). Outcome measures included mean mRS and dichotomous good outcome defined as discharge mRS 0–1 and 0–2. We also performed multivariate ordinal logistic regression with the outcome of discharge mRS and the predictor variable of an error of tPA administration, using NIHSS in the model to control for stroke severity. We repeated these analyses substituting mRS at follow up when available. Secondary outcomes measures included parenchymal hematoma (PH) as defined

by ECASS criteria,(6) any hemorrhage (including systemic bleeding and asymptomatic petechial hemorrhage seen only on MRI-based susceptibility weighted imaging), and in-hospital death.

Statistical analysis was via STATA version 13.0. Statistical significance for intergroup differences was assessed by Pearson χ^2 or Fisher exact test for categorical variables and by Student t or Mann–Whitney U test for continuous variables.

RESULTS

We identified 131 patients treated with systemic IV tPA for a presumptive diagnosis of AIS: 51.2% female, mean age 67.7 years (SD 15.2), and mean presenting NIHSS 9.5 (SD 6.4). Of all patients, 42 (32.1%) were treated at the CSC and 89 (67.9%) were treated at 22 CHs, with no difference in the NIHSS between these groups (Table 1). Of patients treated at a CH, 23 (25.8%) were evaluated by telestroke prior to tPA administration, 43 (48.3%) were evaluated by telephone, 2 (2.2%) were not evaluated by consultation prior to tPA administration; the method of consultation was not known in the remainder (21, 23.6%) due to lack of documentation.

Inclusion/exclusion criteria deviations were: international normalized ratio (INR) > 1.7 in 2 (1.6%) patients, both treated at CH; initial blood pressure undocumented in 45%, which was more common at CHs (64% vs. 4.8%, $p<0.05$); and NIHSS ≥ 4 in 10% (12% at CSC vs 9% at CH, $p=NS$) (Table 2).

There were no tPA reconstitution or dispensing errors. Only prescription and administration errors were observed, and these were found in 64.1% ($n=84$) of all patients: 40.5% of patients at the CSC and 75.3% of CH ($p<0.001$) (Table 2). There was no significant association between sex, age, ethnicity, or NIHSS and the presence of an error. The most frequent prescription error was wrong tPA dosage for weight, which was documented in 43.5% ($n=57$): 19.1% of patients at the CSC and 55.1% at CH ($p<0.001$). Among those with wrong tPA dosage at CH, 31.1% ($n=14$) were due to a body weight discrepancy > 1kg between institutions. Among those receiving wrong tPA dosages, 47.4% ($n=27$) resulted in overdoses (87.5% at CSC and 40.8% at CH, $p=0.01$). Wrong tPA dosages ranged from –16.5mg to 25mg of overdose (mean –0.03mg, SD 4.8). The other prescription and administration errors included: infusion >60 minutes (14%), total dose >90mg (5%), suspension/discontinuation of infusion (5%), tPA wasted in tubing (4%) (resulting in underdosing), incompatible IV tubing or malfunctioning IV pump (4%), and delayed tPA delivery to bedside (4%). One patient received reteplase but suffered no apparent ill effects.

Utilizing the UHC PSN scale, 67.9% ($n=57$) of errors were associated with no harm. Emotional distress or inconvenience was associated with 2 (3.1%) tPA overdoses, specifically minor local IV infiltration of tPA and asymptomatic petechial hemorrhage. Additional treatment was required after 2 (3.1%) tPA overdoses (additional imaging required after asymptomatic petechial hemorrhage). Severe harm was possibly associated with 1 (1.5%) error: tPA underdosing was associated with subsequent unsuccessful mechanical thrombectomy and discharge mRS of 4. Three (4.6%) errors were associated

with death, all after tPA overdose: two due to intraparenchymal hematoma (one requiring hemicraniectomy) and one due to retroperitoneal bleeding.

A discharge mRS was available in 98.5% (n=129) and a follow-up mRS was available in 55.7% (n=73) patients at a mean of 125 days (SD 17.5). There was a strong association between higher NIHSS at admission and worse mRS at follow-up ($p < 0.001$). There was no significant association between presence of error and poor outcome, as measured by dichotomized or mean mRS. PH occurred in 7% of all patients (6.0% with errors, 10.6% without errors, $p = \text{NS}$). In-hospital death occurred in 10.7% overall (8.3% with errors, 14.9% without errors, $p = \text{NS}$). There was no statistical association between tPA overdoses in aggregate or those errors thought to increase risk of PH (overdose for CSC-measured body weight, total dose $> 90\text{mg}$, or infusion > 60 minutes) with observed PH or any systemic bleeding, despite the 3 above-mentioned over-doses associated with hemorrhage and death. There was also no association between hospital type (CSC or CH) and mRS, PH, or mortality (Table 3).

Treatment of stroke mimics was more common at the CSC (9.5% vs 7.9% at CH, $p = \text{NS}$). None of the patients treated for a stroke mimic had PH after tPA. Results were unchanged when restricting outcomes analyses to patients with final diagnosis of stroke.

DISCUSSION

Our study found tPA prescription and administration errors to be very common in our regional stroke system, especially among patients treated at CHs, and despite tPA protocol adherence comparable to other published datasets. The findings show that in spite of a systematic approach to tPA administration by the treatment team, there can still be many errors that affect patient care between the decision to give tPA and actual administration of tPA to the patient.

Almost half of these errors were incorrect tPA dosage for body weight, usually due to an inaccurate recorded body weight at CH. In our collective experience, body weight is frequently estimated by CH providers but this information was not specifically recorded in our dataset. About half of these dosage errors resulted in overdose, and even more concerning, three of the overdoses were associated with death. Though we were not able to demonstrate a statistical effect of these preventable errors overall on outcomes in this small data set, they clearly have potential adverse effect in individual cases and should be carefully avoided. Alternate tPA protocols have been studied but there is no data on the effect of tPA infusion times > 60 minutes, tPA bolus > 2 minutes, and interruption in tPA infusion in AIS. A higher tPA dose of 1.1 mg/kg up to 6 hours from onset of symptoms was associated with a high rate of PH,⁽⁶⁾ and a reduced tPA dose of 0.6 mg/kg demonstrated comparable outcomes to 0.9 mg/kg .⁽⁸⁾

Accurate tPA dosing may be complicated by the fact that it is available in both 100mg and 50mg vials. The 100mg vial contains more than the maximal tPA dose for stroke which can result in inadvertent over-dosing, particularly during patient hand-offs during transport. For this reason, the manufacturer recommends wasting the excess tPA after reconstitution, prior

to administration.(2) Moreover, if the 50mg vial is used in patients exceeding 55kg, a second vial is needed to continue the infusion. Both of these issues represent additional complexity for transport teams. It may be important for CH's to utilize specific dosing and reconstitution protocols, such as those provided by the Utah Bureau of EMS in the Stroke Toolkit written for Stroke Receiving Facilities.(9)

Previous studies have looked at tPA inclusion/exclusion criteria errors and dosing errors in the context of NINDS(1) and ECASS-3(10) trial protocol deviations and found them in the range of 30 – 44%. Timing-related errors were more common than non-timing protocol deviations,(11–13) which include incorrect tPA dosing or timing, early IV heparin or anti-thrombotic use, inadequate blood pressure management, and administration to patients with clinical or laboratory contraindications.(11,13,14) The lower frequency of inclusion/exclusion criteria errors in this study may reflect improving education among CSCs and CHs since earlier datasets.

There are conflicting data to suggest whether pre-treatment neurology consultation is(12) or is not(11) associated with decreased protocol deviation; other data suggest that even with neurologic consultation, “drip-and-ship” practice is associated with more protocol deviations than treatment at a CSC.(13) Likewise, there are conflicting data to suggest that protocol deviations are(14,15) or are not(13) associated with outcomes.

Multiple studies have demonstrated favorable safety data and outcomes in stroke mimics inadvertently treated with tPA. Reported rates of misdiagnosis of stroke mimic as AIS at the time of tPA treatment are in the range of 1 – 14%, with rates of symptomatic ICH among tPA-treated stroke mimics at 0 – 1.0% (16–18). Our data support the idea that in cases of possible AIS in which the diagnosis is uncertain, there is a minimal risk of complication associated with tPA,(19) though it is an expensive therapy when not needed.(20)

Until quite recently, tPA protocols(3) were based on the indications and contraindications established by the NINDS(1) and ECASS-3(10) trials. Additional data have shown safety and efficacy in selected AIS patients with minor or resolving stroke symptoms,(21) seizure at onset,(22) acute myocardial infarction within previous 3 months,(23) major surgery or serious trauma within previous 14 days, and recent gastrointestinal or urinary tract hemorrhage within previous 21 days.(24–26) This has lead to their reclassification as relative exclusion criteria in the most recent 2013 AHA guidelines(7) and removal as contraindications in the most recent alteplase package insert.(27)

This study has several important limitations, particularly due to its retrospective nature and resulting lack of complete record availability, so our results may not represent the true incidence of tPA medication errors. We could not ascertain who documentation (nurse vs pharmacist) prepared the tPA at CHs due to lack of. Similarly, we could not determine if blood pressure and weight were not measured pre-tPA at the CHs or simply weren't documented. We did not have the sample size to determine if there were particular types of errors that are more likely to lead to worse outcomes than others. Outcomes were not determined systematically at the same time for all patients. Strengths include the excellent

recovery of pharmacy records and the use of standard methodology of reporting pharmacy errors.

CONCLUSION

tPA prescription and administration errors in patients with AIS are very common in our large, regional stroke system, particularly among patients treated as transfer “drip-and-ships”. Although in this small population it is reassuring that errors were not significantly associated with overall outcomes including PH, any preventable errors associated with adverse outcomes are serious, particularly those that potentially lead to over- or under-dosing of tPA, and should be carefully avoided. Other larger datasets may show that some error types are more likely to cause poor outcome than others. CSCs should include tPA prescription and administration education and quality assurance mechanisms within their systems in order to reduce avoidable, systematic errors and reduce variance in delivery of ideal acute stroke care.

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Table 1

Demographics including vascular risk factors

Demographics	All patients (n = 131)	Treated at CSC (n = 42)	Treated at CH (n=89)
Age - years (SD)	67.7 ±15.2	67.4 ±16.8	68.0 ±14.5
Male - no. (%)	64 (48.9)	19 (45.2)	45 (50.6)
NIHSS at presentation (SD)	10.3 ±6.6	9.9 ±5.3	11 ±7.6
Past Medical History - no. (%)			
Atrial Fib/Atrial Flutter	35 (26.7)	8 (19.0)	27 (30.3)
Hypertension	90 (68.7)	26 (29.2)	63 (70.8)
Diabetes Mellitus	31 (23.7)	5 (11.9)	26 (29.2)*
Coronary Artery Disease	26 (19.9)	8 (19.1)	18 (20.2)
CHF (Ejection fraction <35%)	12 (9.2)	4 (9.5)	8 (9.0)
Hyperlipidemia	39 (37.4)	15 (35.7)	34 (38.2)
Ischemic Stroke	22 (16.8)	9 (21.4)	13 (14.6)
TIA	8 (6.1)	5 (11.9)	3 (3.4)
Valvular heart disease	10 (7.6)	2 (4.8)	8 (9.0)
Smoking	27 (21.1)	12 (29.3)	15 (17.2)

CSC = comprehensive stroke center; CH = community hospital; NIHSS = National Institutes of Health Stroke Scale; tPA = tissue plasminogen activator; LSN = last seen normal; CHF = congestive heart failure; TIA = transient ischemic attack

*
p < 0.05

Table 2

Comparison of errors (by CSC and CH)

Error Type	All patients (n = 131)	Treated at CSC (n = 42)	Treated at CH (n=89)
INCLUSION/EXCLUSION DEVIATIONS			
Not AIS - no. (%)	11 (8.4)	4 (9.5)	7 (7.9)
INR >1.7 - mean (SD)	1.6 (2)	0	2.3 (2)
Initial blood pressure not available - no. (%)	59 (45.0)	2 (4.8)	57 (64.0)
NIHSS 4 - no. (%)	13 (9.9)	5 (11.9)	8 (9.0)
tPA PRESCRIPTION/ADMINISTRATION ERRORS - no. (%)			
Any tPA dosing/administration error	84 (64.1)	17 (40.5)	67 (75.3)
tPA dose incorrect for weight	57 (43.5)	8 (19.1)	49 (55.1)
CH dose incorrect from incorrect weight	NA	NA	14 (31.1)
Total tPA dose exceeded 90 mg	7 (5.3)	1 (2.4)	6 (6.7)
tPA delivery to bedside > 15 min	5 (3.8)	5 (11.6)	NA
tPA bolus administration > 2 min	3 (2.3)	0	3 (3.4)
tPA infusion duration > 60 min	18 (13.7)	4 (9.5)	14 (15.7)
tPA infusion suspended, stopped early, or too fast	6 (4.6)	2 (4.8)	4 (4.5)
Incompatible or malfunctioning IV pump	5 (3.8)	2 (4.8)	3 (3.4)
tPA wasted in tubing	5 (3.8)	1 (2.4)	4 (4.5)
IV site infiltration	2 (1.5)	1 (2.4)	1 (1.1)
tPA other than alteplase (reteplase)	1 (0.8)	0	1 (1.1)

CSC = comprehensive stroke center; CH = community hospital; AIS = acute ischemic stroke; INR = international normalized ratio; MCA = middle cerebral artery; tPA = tissue plasminogen activator; IV = intravenous

⁺
p < 0.05

Table 3

Outcomes by errors

Outcome Measure	All patients (n=131)	Patients with errors (n=84)	No errors (n=47)	Treated at CSC (n = 42)	Treated at CH (n=89)
Parenchymal hematoma (PH 1/2), * no. (%)	10 (7.6)	5 (6.0)	5 (10.6)	3 (7.1)	7 (7.9)
Any hemorrhage, no. (%)	29 (22.1)	16 (19.1)	13 (27.7)	11 (26.2)	18 (20.2)
mRS at discharge - no. patients in cohort, median mRS (IQR)	129, 3 (1-4)	83, 3 (1-4)	46, 3 (1-4)	41, 3 (1-4)	88, 3 (1-4)
Death, no. (%)	14 (10.7)	7 (8.3)	7 (14.9)	4 (9.5)	10 (11.2)
Good outcome at discharge (mRS 0-1), no. (%)	44 (33.6)	28 (33.3)	16 (34.0)	13 (31.0)	31 (34.8)
Good outcome at discharge (mRS 0-2), no. (%)	57 (43.5)	35 (41.7)	22 (46.8)	16 (38.1)	41 (46.1)

* EC/ASS 1 & 2 definitions.

CSC = comprehensive stroke center; CH = community hospital; mRS = modified Rankin Score; IQR = interquartile range