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Thrombolytic Administration for Acute Ischemic Stroke: What Processes can be Optimized?

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ABSTRACT

Background: The therapeutic benefit of tissue plasminogen activator (tPA) for acute ischemic stroke is proven but extremely time-dependent. Currently, guidelines recommend a < 60 minute door-to-needle time. We identify here factors affecting door-to-needle time of tPA administration for acute ischemic stroke.

Methods: We conducted a retrospective chart review of an emergency department from 2010 to 2013. Inclusion criteria were discharge diagnosis of acute ischemic stroke and tPA administration within 4.5 hours of onset. Exclusion criteria were non-ischemic strokes (transient ischemic attacks, subarachnoid hemorrhage, intracerebral hemorrhage) or those given tPA > 4.5 hours. We used a linear regression model to quantify factor influence and compared tPA administration benchmark times to target benchmark times (median + quartiles).

Results: Among the 71 ischemic stroke patients included, 38 (54%) received tPA within ≤ 60 minutes. Female sex was associated with a door-to-needle time delay of 13.97 minutes (95% CI 3.412 to 27.111). Median benchmark times did not show evidence of delay in any benchmark in comparison with target benchmark times.

Conclusion: Female sex was associated with increased door-to-needle time. Further investigation of these areas may enable optimized workflow, decreased door-to-needle times, and improved patient outcomes.

KEYWORDS

Stroke, Thrombolysis, Emergency department, Workflow

1 | INTRODUCTION

Acute ischemic stroke is the leading cause of disability and the fifth leading cause of death in the United States (1). Intravenous (IV) recombinant tissue plasminogen activator (tPA) as a treatment for acute ischemic stroke has a Class I, Group A level of evidence recommendation from the American Heart Association/American Stroke Association (AHA / ASA) guidelines (2). The therapeutic benefit of tPA is proven but extremely time-dependent. Pooled data from large randomized clinical trials have shown that the therapeutic benefit declines throughout the first 4.5 hours after symptom onset, after which there is no benefit (3, 4). Additionally, it has been shown that each 15-minute reduction in tPA administration time causes the gain of an average equivalent of 1 month of disability-free life (5).

Because of the clear time-dependent benefits of tPA, (AHA / ASA) guidelines on acute ischemic stroke treatment state that the tPA door-to-needle time should be within 60 minutes (2, 6-8). The door-to-needle time is defined as the time from hospital arrival until tPA administration. Additionally, the Target: Stroke initiative outlines more benchmark times, such as door-to-CT (computed tomography) within 25 minutes and door-to-coagulation labs within 45 minutes (6-8). While methods such as advanced pre-hospital notification and acute stroke triage pathways have been shown to decrease door-to-needle time (9-11), best practices are not implemented in many hospitals throughout in the United States (12) and two-thirds of acute ischemic stroke patients still have door-to-needle times over 60 minutes (13). Therefore, further research is required to elucidate factors delaying tPA treatment. The objective of this study is to identify patient factors and workflow steps that are associated with delays in administration of IV tPA in patients presenting with acute ischemic stroke.

2 | METHODS

We conducted a retrospective chart review of patients presenting to an inner-city county emergency department (ED) in the United States from June 2010 to May 2013. All patient data was taken from this hospital's "Get With The Guidelines-Stroke" database, and authors verified patient datapoints and timestamps through individual chart review. Patient inclusion criteria were a discharge diagnosis of acute ischemic stroke and administration of IV tPA within 4.5 hours of symptom onset. Exclusion criteria included patients presenting with intracranial hemorrhage, subarachnoid hemorrhage, a transient ischemic attack, or patients who were given IV tPA after 4.5 hours. tPA after 4.5 hours was used as an exclusion criterion to better identify problems in the tPA administration process for the vast majority of cases, rather than outlier cases for whom the tPA workflow process may not be as widely applicable. Selection of patients is described via Figure 1.

We collected patient demographic factors, clinical factors, and tPA administration timed benchmarks to study their effect on primary and secondary outcomes. Patient demographic factors included age, race/ethnicity, and sex. Clinical factors included method of arrival, onset to arrival time, systolic and diastolic blood pressure, stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), and co-morbidity. We studied 11 tPA administration timed benchmarks based on the "Target: Stroke" initiative: 1) triage done ($\leq$ 1 min); 2) stroke alert paged ($\leq$ 5 min); 3) patient to critical care room ($\leq$ 5 min); 4) emergency physician at bedside ($\leq$ 5 min); 5) neurologist at bedside ($\leq$ 15 min); 6) blood carried to lab ($\leq$ 15 min); 7) head CT performed ($\leq$ 25 min); 8) verbal results of head CT available ($\leq$ 45 min); 9) head CT results in electronic medical record (EMR) ($\leq$ 45 min); 10) complete blood count (CBC), prothrombin time/international normalized ratio/partial thromboplastin time (PT/INR/PTT) results in EMR ($\leq$ 45 min); and 11) tPA ordered ($\leq$ 50 min).

Our primary outcome was door-to-needle time of tPA administration. Data on pre-hospital notification and other secondary outcomes, such as disposition location, were available only for a limited number of patients and therefore were not included in our analysis. Likewise, other limitations (see discussion) prevented analy-

sis of additional secondary outcomes such as in-hospital mortality, ambulation at end of day, ambulation at discharge, and hospital length of stay.

This study was consistent with established methodologic recommendations (14, 15) and was approved by the Baylor College of Medicine Institutional Review Board, which granted a waiver of informed consent for our retrospective analysis.

2.1 | Data Analysis

Door-to-needle time was defined as a categorical variable with two groups: 0-60 minutes (no delay) and 61-270 minutes (delayed administration). We calculated descriptive demographic statistics and standardized mean difference to measure the effect of each feature on whether a patient would have delayed tPA administration.

We built a simple linear regression model to quantify the influence of each patient demographic and clinical factor on door-to-needle time, a continuous response variable. The estimated effect was calculated to determine each variable's impact on door-to-needle time in number of minutes.

Finally, we compared the time for the completion of 11 tPA administration benchmarks in our data to target times set by the AHA / ASA (6) (a benchmark time greater than the AHA / ASA target time would constitute a delay). Benchmark times are reported using minutes and median + quartiles.

Data was analyzed using RStudio version 1.1 (RStudio Inc., Boston, MA).

3 | RESULTS

Patient selection is shown in Figure 1 and demographic and clinical factors are shown for each door-to-needle time group in Table 1. Of 1,181 patients presenting with symptoms of stroke during the study time period of 2010 - 2013, 71 (6.0%) met the inclusion criteria. Of these, 38 (54%) received tPA within ≤ 60 min, while 33 (46%) had a delayed door-to-needle time. Our tPA pop-

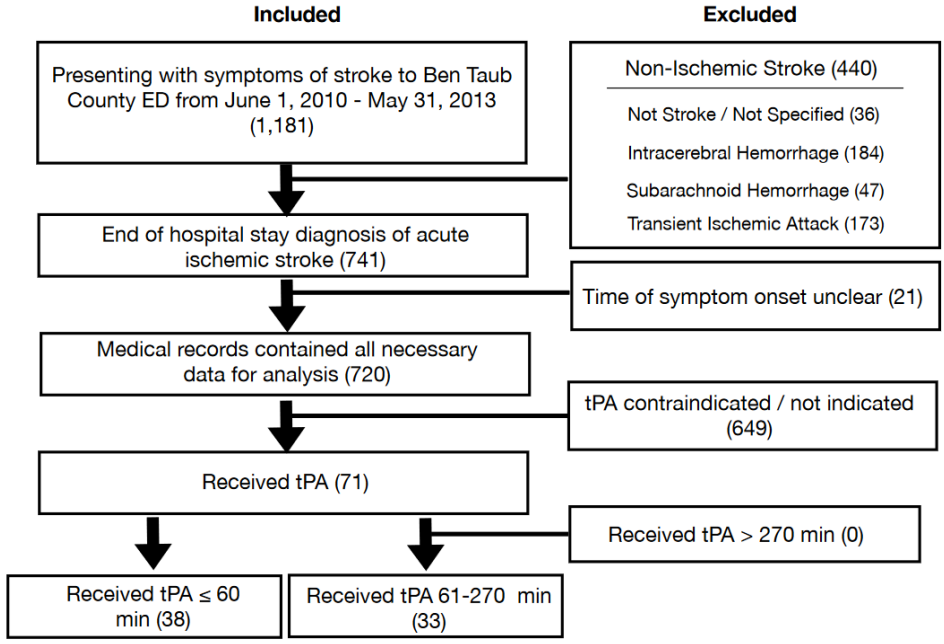

FIGURE 1 Selection of patients

ulation was 49% male, had a mean age of 56 years, and were 48% Hispanic, 35% African American, 13% Caucasian, and 4% other race/ethnicies. Standardized mean difference between groups showed female sex (.377), arrival by emergency medical services transport (.678), systolic blood pressure (.458), atrial fibrillation / flutter (.369), and NIHSS score of 10 – 14 (.426) were highly unbalanced.

Table 2 displays the results of the linear regression, showing the influence and estimated effect of patient demographic and clinical factors on continuous door-to-needle time. Female sex was associated with a total door-to-needle time increase of 14 minutes (95% CI, 3.412 - 27.111) and every per-minute increase in onset-to-arrival time was associated with a mean door-to-needle time increase of .12 minutes (95% CI, 0.00 - .246). Blood pressure, NIHSS score, age, race, emergency medical services transport, and patient comorbidities (e.g. atrial fibrillation / flutter) did not have a significant effect on door-to-needle time in the analysis.

Table 3 shows the comparison of the time taken to complete each of the 11 tPA administration benchmarks with standard target times for each benchmark. Median benchmark times did not show evidence of delay in any benchmark in comparison with target benchmark times.

4 | DISCUSSION

We found a relationship between increased door-to-needle times and female sex, based on the results of Table 1 and Table 2. Our finding of a mean total increase of 14 minutes highlights several challenges. First, for female patients, a urine pregnancy test may be performed prior to therapy because of the risk of uterine bleeding with tPA administration. Historically, tPA usage in pregnancy has been considered a relative contraindication. Earlier reviews of the small number of published case reports on this topic found varied results, from fetal demise to safe maternal and fetal outcomes (16-19). More recent findings and current guidelines leave tPA administration in pregnant patients with acute ischemic stroke up to physician discretion when the benefits of treating moderate or severe stroke outweigh the risks of uterine bleeding (2, 20-22). We suggest the need of further studies on the rates of physician usage of tPA in pregnant patients with acute ischemic stroke, and on the effect of across-the-board urine pregnancy testing on door-to-needle times. In the ED, the mean time to results of a urine pregnancy test available is 7.6 minutes if done at point-of-care and 32.6 minutes if sent to a laboratory (23), which may explain the difference seen in our patient population.

Past studies have shown that there are sex differences in the clinical presentation of acute ischemic stroke, with female patients presenting with fewer classic symptoms such as hemiparesis (24-26). Our findings are in line with studies that show female patients have greater delays in acute ischemic stroke treatment. Additionally, emergency medical services transport was utilized by slightly more male than female patients (55% vs 45%) which may have contributed to the door-to-needle time discrepancy. The causes for these delays are unknown, but it is possible that atypical acute ischemic stroke presentations may be contributing to these delays, as well as the possibility of physician or other provider bias.

While Table 1 shows that other variables, such as systolic blood pressure and atrial fibrillation / flutter, were also imbalanced, linear regression in Table 2 did not find a significant association with delayed door-to-needle time among these variables. Therefore, we view the statistically significant 14 minute mean door-to-needle increase for female sex as the most important finding from these analyses. Additionally, based on the results in Table 2, we technically found a statistically significant relationship between increased door-to-needle times and onset-to-arrival times. Time from symptom onset to hospital arrival is an established factor in eligibility for ischemic stroke interventions, such as tPA administration. The p value in our study of .049, however, is borderline at best, and the confidence interval contains zero. We therefore interpret this result conservatively and treat it as a non-significant result. In other literature, a study of 413,147 ischemic stroke patients from 2003 – 2006 found that over 25% of patients with ischemic stroke

Patient Factors*	Door to Needle Time Group (%)		Standardized Mean Diff
	0-60 min (n=38)	61-270 min (n=33)	(absolute value)
Age (years), mean (SD)	56.92 (13.93)	55.70 (10.04)	0.101
Female, sex	42.1% (n=16)	60.6% (n=20)	0.377
Race			
Caucasian	(S†)	15.15% (n=5)	0.139
African American	34.2% (n=13)	36.36% (n=12)	0.045
Hispanic	50% (n=19)	45.45% (n=15)	0.091
Asian	S†	S†	0.024
Other	S†	0.00% (n=0)	0.233
NIHSS, median (IQR)	10 (7-15)	9 (6-16)	
0-9	42.11% (n=16)	57.58% (n=19)	0.313
10-14	28.95% (n=11)	12.12% (n=14)	0.426
>14	28.95% (n=11)	30.30% (n=10)	0.030
Systolic BP, mm Hg mean (SD)	153.18 (28.31)	168.48 (37.89)	0.458
Diastolic BP, mm Hg mean (SD)	89.58 (14.77)	93.88 (21.22)	0.235
Onset to arrival time, mean (SD)	75.95 (46.11)	73.12 (61.39)	0.052
Arrival by EMS	68.4% (n=26)	36.36% (n=12)	0.678
Comorbidities			
AFib/flutter	S†	S†	0.369
Hypertension	65.79 (n=25)	78.79% (n=26)	0.294
CAD	13.16% (n=5)	15.15% (n=5)	0.057
Carotid stenosis	(S†)	0.0% (n=0)	0.232
Diabetes mellitus	34.21% (n=13)	36.36% (n=12)	0.045
Dyslipidemia	28.95% (n=11)	24.24% (n=8)	0.107
Heart failure	S†	S†	0.245
Migraine	S†	0.0% (n=0)	0.233
Obesity/overweight	S†	0.0% (n=0)	0.233
Previous AIS	35.58% (n=12)	36.36% (n=12)	0.101
Sickle cell	0.0% (n=0)	S†	0.250
Smoking	23.68% (n=9)	30.3% (n=10)	0.150

*Abbreviations: NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; EMS, emergency medical services; BP, blood pressure; AFib, Atrial fibrillation; CAD, coronary artery disease; AIS, acute ischemic stroke. S† number suppressed to preserve patient confidentiality.

TABLE 1 Comparison of Characteristics of Patients in Timely and Delayed Door-to-Needle Time.

do arrive within the window for tPA administration (27). More recently, another study from the early containment phase of the coronavirus-19 pandemic did not find any evidence of delayed door-to-needle times (28), despite differences in onset-to-arrival times between pre-covid and covid groups.

We also did not find evidence of a delay in any specific benchmark, based on crude comparison of median benchmark times with target times in Table 3. While the AHA / ASA Target: Stroke initiative has provided target

Patient Factors*	Minutes Faster, min (95% CI)	*p*
Age, per year decrease	-0.4 (-0.94 to 0.14)	0.15
Sex		
Male	14.0 (3.4 to 27.1)	0.037
Female	0 [Reference]	
Arrival Mode		
EMS	6.5 (-11.5 to 24.5)	0.48
Non-EMS	0 [Reference]	
NIHSS		
0-9	0 [Reference]	
10-14	15.4 (-1.9 to 32.6)	0.08
>14	12.3 (-3.1 to 27.7)	0.12
Systolic BP (per 1 mmHg increase)	- 0.0 (-0.2 to 0.2)	0.92
Diastolic BP (per 1 mmHg increase)	0.0 (-0.3 to 0.4)	0.80
OTA time per min decrease	0.1 (0.0 to 0.2)	0.049
Comorbidities		
AFib/flutter	12.2 (-7.1 to 31.4)	0.21
No AFib/flutter	0 [Reference]	
Hypertension	0.0 (-15.1 to 15.1)	0.99
No hypertension	0 [Reference]	
CAD	7.2 (-12.3 to 26.6)	0.47
No CAD	0 [Reference]	
Carotid stenosis	19.2 (-38.1 to 76.6)	0.51
No carotid stenosis	0 [Reference]	
Diabetes mellitus	- 7.2 (-21.3 to 6.8)	0.31
No diabetes	0 [Reference]	
Dyslipidemia	-0.9 (-16.2 to 14.4)	0.91
No dyslipidemia	0 [Reference]	
Heart failure	- 11.2 (-35.4 to 13.1)	0.36
No heart failure	0 [Reference]	
Migraine	30.4(-26.7 to 87.4)	0.29
No migraine	0 [Reference]	
Obesity/overweight	15.2 (-42.3 to 72.6)	0.60
No obesity/overweight	0 [Reference]	
Previous AIS	1.6 (-12.7 to 15.9)	0.82
No previous AIS	0 [Reference]	
Sickle cell	-30.5 (-87.5 to 26.6)	0.29
No sickle cell	0 [Reference]	
Smoking	- 2.7 (-18.0 to 12.6)	0.72
No smoking	0 [Reference]	

*Abbreviations: DOOR-TO-NEEDLE, door-to-needle; EMS, emergency medical services; NIHSS, National Institutes of Health Stroke Scale; OTA, onset-to-arrival; BP, blood pressure; AFib, Atrial fibrillation; CAD, coronary artery disease; AIS, acute ischemic stroke.

TABLE 2 Linear Regression Analysis of Patient Factor Effect on Door-to-Needle Time

Benchmark*	Time to Complete Benchmark (Min)		Target Time (min)
	Median	Quartiles [Q1, Q3]	
Triage Done	0.0	[0.0, 3.3]	≤ 1
Stroke Alert Paged	2.0	[1.0, 6.3]	≤ 5
Patient to CC Room	3.0	[1.0, 9.3]	≤ 5
EM Faculty at Bedside	4.0	[2.0, 8.0]	≤ 5
Neurologist at Bedside	5.0	[2.0, 11.0]	≤ 15
Blood Carried to Lab	8.5	[5.0, 15.0]	≤ 15
Head CT Performed	15.0	[10.0, 21.3]	≤ 25
Verbal Results of Head CT	18.5	[11.0, 24.3]	≤ 45
Head CT Results in Epic	29.5	[23.0, 40.3]	≤ 45
CBC, PT/INR/PTT in EMR	37.5	[28.4, 59.6]	≤ 45
tPA Ordered	38.7	[30.4, 55.0]	≤ 50

*Abbreviations: tPA, tissue plasminogen activator; DOOR-TO-NEEDLE, door-to-needle; CC, critical care; EM, emergency medicine; CT, computed tomography; EMR, electronic medical record; CBC, complete blood count; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time.

TABLE 3 Comparison of individual tPA administration benchmarks times with target time for each benchmark

times for each benchmark (6), further research is needed to identify key "bottlenecks" causing delays in tPA workflow. Such findings would have important clinical relevance because they would demonstrate where specific delays are occurring in the tPA administration workflow, providing an opportunity for targeted optimization to decrease door-to-needle time.

Many quality improvement programs have been effective in reducing door-to-needle times. A notable example is the Helsinki stroke thrombolysis model (29), which achieved a median door-to-needle time of 20 min in Finland. This model has been implemented in other settings such as Melbourne, Australia, where it achieved a 25 minute reduction in overall median door-to-needle time (from 61 minutes to 46 minutes) (30), and Christchurch, New Zealand, where overall median door-to-needle was reduced from 87 minutes to 40 minutes (31). The Helsinki protocol includes 1) ambulance pre-notification mobilizing the stroke team to receive the patient; 2) patients moved from triage to CT while still on the ambulance stretcher; and 3) delivery of tPA in CT immediately following imaging. The success of this model when transferred from Europe to other continents underscores the potential for similar results to be attainable in other settings. Therefore, future research should also consider whether features of this model are transferrable to settings such as the US and Canada and evaluate their impact, if any, on door-to-needle times.

Our study is limited by the small sample size, use of a single ED location, and the retrospective design. Nonetheless, our results are clear and consistent with prior studies. While the sample size of 71 ischemic stroke patients is too small to act as a nationally generalizable sample, the number does reflect the full population of ischemic stroke patients presenting to Ben Taub County Hospital ED over a three-year period and was large enough to permit valid statistical analysis. Second, with respect to the use of a single ED, it is true that differences in hospital EMR systems, laboratory resources, staffing ratios, and general level of expertise (e.g. whether the hospital had an in-house stroke unit) may significantly impact patient care. However, by focusing on a single ED, we reduce variations that may lead to improper analysis, as different EDs may use different benchmarks for tPA administration.

The limitations introduced by using a retrospective

study design merit additional discussion. Data recorded on pre-hospital notification was incomplete and thus removed from our analysis. Older and more recent studies however have found an association between pre-hospital notification and arrival via emergency medical services with decreased door-to-needle times (9, 11, 32-37). Provider bias may also be a factor in these results, as patients coming to the ED by ambulance are often treated with a greater sense of urgency which may contribute to faster door-to-needle times (38). Third, although it is possible that female patients presented with less classic signs and symptoms which caused a more delayed door-to-needle time, the scope of our chart review was limited to comparisons of overall National Institutes of Health Stroke Scale score and not individual variability in signs and symptoms.

Additionally, the 2013 AHA / ASA guidelines were updated in 2018 and 2019 (2, 39) which may have modified current provider practices. While most guidelines were either unchanged, reworded for clarity, or had their level of evidence reclassified, two new recommendations for ischemic stroke are worth note. First, guideline 1.5.3 proposes it may be reasonable to establish a secondary goal of door-to-needle times within 45 minutes in $\geq$ 50% of patients with AIS who were treated with IV alteplase. This is based on a study of 16,901 patients with ischemic stroke (treated with IV alteplase 4.5 hours of symptom onset) where 30.4% were treated 45 minutes after hospital arrival (40). Second, guideline 1.5.5 recommends that "multicomponent quality improvement initiatives, which include ED education and multidisciplinary teams with access to neurological expertise, are recommended to safely increase IV thrombolytic treatment." This recommendation is based on the US cluster-randomized INSTINCT trial (Increasing Stroke Treatment Through Interventional Change Tactics), which demonstrated increased rates of alteplase use among the intervention group (41). While these recommendations have the potential to alter current and future practices with respect to the door-to-needle time workflow, they do not influence our findings for the years 2010 – 2013. Therefore, we recommend that comparison of our findings to more recent data would be a valuable direction for future research.

As a final note, stroke severity is an important confounder of unadjusted door-to-needle time analysis as increased severity can increase the likelihood of earlier presentation and worse outcome (42). Our study, however, focused specifically on potential delays in the workflow of tPA administration, not outcome differences. Better adjustment for confounders and a more thorough study design would be necessary to evaluate whether there is such an association. Nevertheless, there is already strong evidence that delayed door-to-needle times leads to poorer outcomes (4, 5, 13, 42, 43).

In conclusion, we found that female sex is associated with delayed door-to-needle time but did not find evidence of delays in any specific tPA administration benchmark. Further investigation into these areas may allow for optimization of workflow leading to decreased door-to-needle times and improved patient outcomes.

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