Research Report

Pharmacist Participation in Acute Ischemic Stroke Decreases Door-to-Needle Time to Recombinant Tissue Plasminogen Activator

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Abstract

Background: Pharmacists are an important member of the stroke team and aid in obtaining medication and medical history, providing education, managing blood pressure, reviewing exclusion criteria for recombinant tissue plasminogen activator (rtPA), and facilitating reconstitution and administration of rtPA. **Objective:** To determine if pharmacist presence at bedside during acute ischemic stroke resulted in a reduction in door-to-needle (DTN) times. **Methods:** This was a retrospective cohort study between January 1, 2011 and December 31, 2015 of patients who received rtPA for acute ischemic stroke in either the emergency department or hospital. **Results:** Of the 125 included patients, 45 patients (36%) had a pharmacist present (PharmD group) and 80 patients (64%) did not (no PharmD group). Median DTN time was significantly shorter in the PharmD group: 48 minutes versus 73 minutes in the no PharmD group ($P < 0.01$). The goal of DTN ≤60 minutes was met in 71% of patients in the PharmD group compared to 29% ($P < 0.01$). Pharmacist at the bedside was the only factor found to be independently associated with reduction DTN time (βcoefficient −23.5 minutes, 95% confidence interval [95% CI] −38.6 to −8.50 minutes). **Conclusion:** A pharmacist at the bedside of emergency department or in-patient stroke codes reduced DTN time by a median of 23.5 minutes after adjusting for confounding factors and increased the percentage of patients meeting DTN goal time of ≤60 minutes by 49%. These findings support the inclusion of a stroke-competent pharmacist in the bedside response team for acute ischemic stroke patients.

Keywords

stroke, pharmacist/physician issues, thrombolytics, clinical pharmacy, neuropharmacology

Introduction

Stroke is the fifth leading cause of mortality in the United States. Approximately 800 000 people experience a stroke annually, equivalent to 1 person every 40 seconds. By 2030, an increase in stroke prevalence of 20.5% is expected compared with 2012.[1] The American Heart Association/American Stroke Association (AHA/ASA) guidelines for the early management of acute ischemic stroke recommend eligible patients receive recombinant tissue plasminogen activator (rtPA) within 60 minutes of hospital arrival.[2] Door-to-needle (DTN) time, defined as time from hospital presentation to rtPA bolus, is an essential target and benchmark for care, due to loss of neurons associated with delay in treatment.[2] It is estimated that for each minute that a stroke goes untreated, 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated fibers are lost, highlighting the importance of timely interventions.[3] Furthermore, pooled data from 6 clinical trials has demonstrated that treatment with rtPA within 90 minutes of stroke symptom onset is associated with a favorable outcome at 90 days.[4] Despite these findings, less than one-third of patients receive rtPA within the goal DTN time of ≤60 minutes.[5] Therefore, it is essential to identify strategies to decrease time to treatment of ischemic stroke.

Pharmacist contributions to an interdisciplinary team in a critical care environment have been well-documented, specifically involving medication information, drug interactions, and therapeutic drug monitoring.[6] Furthermore, pharmacist presence on an interdisciplinary team can also decrease rates of medication administration errors, adverse drug events, and even hospital mortality rates.[6,7] During an acute ischemic stroke, a pharmacist may be involved in

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such activities as taking a medication history, past medical history, participating in patient and/or family education regarding rtPA risks and benefits, evaluating inclusion and exclusion criteria for rtPA, managing blood pressure, and reconstitution and administration of rtPA. With an increase in use of direct oral anticoagulants and complexity of medication histories, pharmacist presence and expertise is especially valuable in evaluating potential drug interactions with rtPA.[8] The purpose of this study was to determine the impact of pharmacist presence at bedside during an acute ischemic stroke in reducing DTN times.

Methods

Study Design

This was a retrospective, single-centered cohort study of patients for whom a stroke code was activated between January 1, 2012 and December 31, 2015 at an academic medical center with primary stroke center designation. Institutional review board approval was obtained prior to patient enrollment.

The primary endpoint of this study was to determine the difference in DTN times between patients who received rtPA for acute ischemic stroke with a pharmacist at the bedside compared with patients without a pharmacist at the bedside. Secondary endpoints included the proportion of patients in each group that met DTN goal ≤60 minutes and ≤45 minutes, door-to-imagining time (DTI), imaging-to-needle (ITN) time, intensive care unit (ICU) and hospital length of stay (LOS), hospital and 90-day mortality, discharge and 90-day modified Rankin score (mRS) and National Institutes of Health Stroke Scale (NIHSS), and symptomatic hemorrhagic conversion.

Participants and Setting

Patients either presented to the emergency department (ED) with stroke symptoms or experienced a stroke while admitted to an inpatient unit. Included patients were those ≥18 years of age who received 0.9 mg/kg rtPA (based on actual body weight; up to 90 mg) within 4.5 hours of stroke symptom onset. Patients were excluded for the following reasons: transfer to our center from an outside hospital, intra-arterial rtPA only, missing or incomplete documentation of arrival time, DTN time or rtPA administration time. Patients were treated at the discretion of an attending neurologist in accordance with treatment guidelines.[2]

Patients were dichotomized according to whether a stroke-competent pharmacist was present at the bedside or not. All clinical and inpatient pharmacists and pharmacy residents undergo stroke training on an annual basis and must pass a case-based and hands-on exam to determine competence. Monday through Friday the stroke pager is covered from 7 AM to 9:30 PM by the following stroke-competent pharmacists: neurosciences ICU pharmacist (7 AM to 9:30 AM ED strokes; inpatient strokes until 1 PM), ED pharmacist (ED strokes 9:30 AM to 6 PM), or the PM ICU pharmacist (ED strokes from 6 PM to 9 PM; inpatient strokes from 1 PM to 9:30 PM). From 9:30 PM to 7 AM, the inpatient pharmacist is available for questions but does not report to the bedside. Stroke codes are covered by pharmacy residents who respond to the bedside on weekends and holidays from 6:30 AM to 9 PM. Due to staff turnover in 2012, there was a gap in bedside pharmacist coverage for stroke codes. Stroke-competent pharmacists are trained to evaluate rtPA contraindications, elicit and review medical histories and medication lists, manage blood pressure, calculate the rtPA dose, reconstitute and administer rtPA with the bedside nurse, counsel patients and/or family members on the risks and benefits of thrombolytic administration, and monitor the patient after rtPA administration. Pharmacist presence was confirmed through review of interventions and note documentation in the electronic medical record. rtPA is housed in stroke kits in the ED and neurosciences ICU automated dispensing units and is prepared and administered at the bedside by the nurse if a pharmacist is not present.

Data were extracted from the electronic medical record (Epic, Madison, WI) for patients meeting inclusion criteria. Baseline demographics included age, sex, and race. The following stroke-related variables were collected: baseline and peak systolic and diastolic blood pressure, antihypertensive treatment, baseline severity of illness according to assessment of NIHSS and mRS, weight, and rtPA dose. Time parameters included stroke symptom onset, patient arrival time to the ED, computed tomography (CT) completion, and rtPA administration. Past medical history of hypertension, end stage renal disease, hyperlipidemia, coronary artery disease, diabetes, stroke, cancer, atrial fibrillation, and congestive heart failure were also collected.

Statistical Analysis

Baseline characteristics were described using mean, standard deviation, median, interquartile range (IQR), and percentages. Continuous parametric variables were compared using a *t* test. Continuous nonparametric data were analyzed utilizing the Mann-Whitney *U* test. Chi-square test or Fischer's exact test were used to compare categorical variables. A P value <0.05 was considered significant in the univariate analysis.

A multivariate linear regression was conducted to assess the change in DTN time associated with pharmacists at the bedside, while accounting for other confounding variables. Variables from the univariate analyses with a P value ≤ 0.2 and variables that were found to be significant in prior studies were evaluated for inclusion into the multivariate analysis.[9,10] The final multivariable linear regression model only

Table 1. Baseline Demographics.

Characteristic	PharmD Group, n = 45	No PharmD Group, n = 80	*P*
Age (years), median (IQR)	70 (60-78)	66.5 (54-79)	0.36
Male gender, n (%)	23 (51.1)	44 (55)	0.68
Weight (kg), mean ± SD	89.0 ± 32.8	83.9 ± 16.6	0.25
Race, n (%)			0.25
White	26 (57.8)	36 (45)	
African American	14 (31.1)	38 (47.5)	
Hispanic	4 (8.9)	5 (6.3)	
Asian	1 (2.2)	0 (0)	
Unknown	0 (0)	1 (1.3)	
Comorbidities, n (%)			
Atrial fibrillation	7 (15.6)	10 (12.5)	0.63
Chronic kidney disease	3 (6.7)	12 (15)	0.17
Diabetes	11 (24.4)	18 (22.5)	0.81
Heart failure	5 (11.1)	13 (16.3)	0.43
Hyperlipidemia	21 (46.7)	32 (40)	0.47
Hypertension	31 (68.8)	58 (72.5)	0.67
Malignancy	4 (8.9)	7 (8.8)	>0.99
Stroke	11 (24.4)	21 (26.3)	0.82
Year, n (%)			
2011	4 (8.9)	25 (31.3)	<0.01
2012	0 (0)	12 (15)	<0.01
2013	9 (20.0)	10 (12.5)	0.26
2014	21 (46.7)	7 (8.8)	<0.01
2015	11 (24.4)	26 (32.5)	0.34
Baseline SBP (mm Hg), mean ± SD	142 ± 27	146 ± 27	0.40
Baseline DBP (mm Hg), mean ± SD	80 ± 21	80 ± 18	0.96
Antihypertensive use, n (%)	10 (22.2)	13 (16.3)	0.41
NIHSS, median (IQR)	9 (4-17)	9 (5-15)	0.99
Stroke in ED	43 (95.6)	75 (93.8)	0.67
Weekend presentation, n (%)	4 (8.9)	26 (32.5)	<0.01
Dayshift presentation, n (%)	44 (97.8)	49 (61.3)	<0.01
rtPA dose (mg), median (IQR)	75 (62-90)	76 (67-87.5)	0.88

Abbreviations: IQR, interquartile range; SD, standard deviation; DBP, diastolic blood pressure; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure; ED, emergency department; rtPA, recombinant tissue plasminogen activator.

retained the variables which significantly affected the model ($P < 0.05$). STATA version 12 (College Station, TX) was used for data analysis.

Results

During the study period, 201 patients received rtPA for acute ischemic stroke, of which 125 (62.2%) were included in the study. The most common reason for exclusion were outside hospital transfers, where rtPA was initiated prior to arrival (n = 46), followed by incomplete documentation of time data (n = 17), rtPA administration >4.5 hours after symptom onset (n = 3), or other reason (n = 10). Of the 125 patients meeting inclusion criteria, 45 patients (36%) had a pharmacist at the bedside (PharmD group) and 80 patients (64%) did not (no PharmD group). Patients were similar at baseline with regard to age, gender, race, and comorbid conditions (Table 1). Weekend presentation occurred more often in the no PharmD group (8.9% vs 32.5%, $P < 0.01$), while daytime presentation was more common in the PharmD group (97.8% vs 61.3%, $P < 0.01$).

The primary endpoint of median DTN time was significantly shorter in the PharmD group at 48 minutes (IQR 36-65 minutes) compared with 73 minutes (IQR 58-97.5 minutes) in the no PharmD group (difference 25 minutes, $P < 0.01$, Figure 1). This difference was observed most clearly in the median change in ITN time (28.5 minutes [IQR 22-42.5 minutes] PharmD group vs 55.5 minutes [IQR 42-70.5 minutes] no PharmD group, $P < 0.01$). Median DTI times were not affected by the presence of a pharmacist (16 minutes [IQR 10-21 minutes] PharmD group vs 16 minutes [IQR 8-25 minutes] no PharmD group, $P = 0.85$). The goal

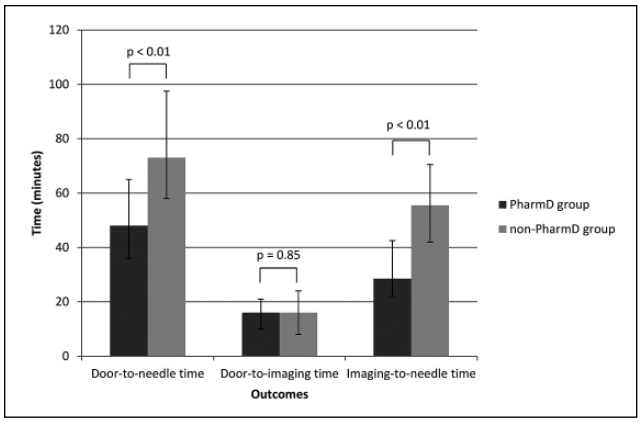

Figure 1. Pharmacist impact on median door-to-needle, door-to-imaging, and imaging-to-needle times.

of DTN ≤60 minutes was met in 71.1% of patients in the PharmD group compared with 28.8% of patients in the no PharmD group ($P < 0.01$, Table 2).

In order to assess the impact of a pharmacist at the bedside without confounding factors related to the stroke service and nursing availability, we analyzed DTN times during the dayshift only (0700 to 1900). This analysis (n = 79) resulted in median DTN times of 47 minutes (IQR 36-57 minutes) in the PharmD group compared with 67 minutes (IQR 56.5-89) in the no PharmD group ($P < 0.01$). When also eliminating weekends and retaining only patients presenting during the dayshift on weekdays (n = 63), similar DTN time results were found (median 47.5 minutes [IQR 36-61 minutes] PharmD group vs 65 minutes [IQR 56-91 minutes] no PharmD group, $P < 0.01$).

Secondary endpoints are displayed in Table 2. There was no difference in hemorrhagic conversion between groups (11.1% PharmD group vs 7.6% no PharmD group, $P = 0.51$). In-hospital and 90-day mortality were not different between groups. Discharge mRS and NIHSS were also similar between groups. At 90 days, patients had similar mRS scores (2 [0-4] PharmD group vs 2 [1-4] no PharmD group, $P = 0.84$). There was a nonsignificant reduction in 90-day NIHSS in the PharmD group (0 [0-0] PharmD group vs 5 [0-5] no PharmD group, $P = 0.05$); however, only 42 patients (PharmD group n = 17; no PharmD group n = 25) had NIHSS scores available at 90 days. There was no difference in ICU or hospital LOS, though both were numerically lower in the no PharmD group (Table 2).

The following variables were included in the multivariate linear regression analysis to explore factors associated with DTN time: weekend presentation, dayshift presentation, year, and pharmacist at the bedside (Table 3). Pharmacist at the bedside was the only factor found to be independently associated with reduction DTN time (β coefficient −23.5 minutes, 95% confidence interval [95% CI] −38.6 to −8.50 minutes). Multicollinearity between these variables was also examined, revealing a mean variance inflation factor of 1.19, suggesting that the benefit of pharmacist presence is not confounded by other factors associated with dayshift or weekday presentation.

Discussion

Our study indicates that pharmacist presence in the management of acute ischemic stroke is an independent predictor lower DTN times. This benefit was most apparent in the ITN time, when decision making after the CT results occur. At our institution, pharmacists evaluate rtPA contraindications, elicit and review medical histories and medication lists, manage blood pressure, calculate the rtPA dose, reconstitute and administer rtPA with the bedside nurse, and counsel patients and/or family members on the risks and benefits of thrombolytic administration with the stroke team. These activities contributed to a reduction in median DTN times by 25 minutes in the univariate analysis; after multivariate linear regression adjusting for year, daytime and weekend presentation, pharmacists were the only predictive factor associated with reduction in DTN time in the model. After examining multicollinearity and performing a subgroup analysis of weekday shift presentation, this benefit remained, thus eliminating confounding due to neurology team or nursing availability. This study supports utilization of pharmacists as members of the stroke response team to optimize DTN goal attainment in acute ischemic stroke.

A 2014 study by Fonarow and colleagues[11] examined DTN times in the setting of the Target: Stroke national quality improvement initiative and effect on outcomes in 71 169 patients. Prior to the quality improvement initiative, participating Get With the Guidelines—Stroke hospitals (n = 27 319 preintervention) demonstrated a median DTN time of 77 minutes (95% CI 60-98 minutes), with 26.5% patients (95% CI 26.0%-27.1%) meeting the DTN goal of ≤60 minutes. The quality improvement initiative included prehospital notification by emergency responders, a stroke team–based approach to evaluation, treatment, and notification; use of tools and protocols, and prompt feedback on performance. Following the quality improvement initiative implementation (n = 43 850), the median DTN time was reduced to 67 minutes (95% CI 51-87 minutes, $P < 0.01$), with 41.3% patients (95% CI 40.8%-41.7%, $P < 0.01$) meeting DTN ≤60 minutes. Postintervention patients also demonstrated decreased mortality (9.93% vs 8.25%, odds ratio [OR] 0.89, 95% CI 0.83-0.94, $P < 0.01$), increased discharge to home (37.6% vs 42.7%, OR 1.14, 95% CI 1.09-1.19, $P < 0.01$), and decreased symptomatic intracranial hemorrhage within 36 hours (5.68% vs 4.68%, OR 0.83, 95% CI 0.76-0.91, $P < 0.01$). Our study built on all these interventions with the addition of a pharmacist to the stroke team and demonstrated that a 71.1% of patients met DTN

Table 2. Secondary Outcomes.

	PharmD Group, n = 45	No PharmD Group, n = 80	*P*
DTN goal ≤60 minutes met, n (%)	32 (71.1)	23 (28.8)	<0.01
DTN ≤45 minutes met, n (%)	20 (44.4)	7 (8.8)	<0.01
DTN by year, median minutes (IQR)			
2011	105 (93.5 – 123)	67 (58 – 85)	<0.01
2012	0 (0)	92.5 (61 – 114)	n/a
2013	57 (53 – 74)	96 (85 – 129)	<0.01
2014	38 (30 – 51)	68 (60 -88)	<0.01
2015	48 (42 – 65)	68 (54 – 97)	0.03
Hemorrhagic conversion, n (%)	5 (11.1)	6 (7.6)	0.51
In-hospital mortality, n (%)	5 (11.1)	9 (11.3)	0.98
90-day mortality, n (%)	10 (22.2)	12 (15)	0.32
Discharge mRS, median (IQR)	3 (0 – 5)	3 (1 – 4)	0.85
Discharge NIHSS, median (IQR)	3 (0 – 11)	4 (0 – 10)	0.71
90-day mRS,[a] median (IQR)	2 (0 – 4)	2 (1 – 4)	0.84
90-day NIHSS,[b] median (IQR)	0 (0 – 0)	5 (0 – 5)	0.05
ICU LOS (days), median (IQR)	3 (2 – 9)	2 (2 – 4)	0.06
Hospital LOS (days), median (IQR)	6 (3 – 13)	4 (3 – 8)	0.09

Abbreviations: DTN, door-to-needle time; mRS, modified Rankin score; IQR, interquartile range; ICU, intensive care unit; ITN, imaging-to-needle time; LOS, length of stay; NIHSS, National Institute of Health Stroke Score.
[a]n = 92 (PharmD group n = 17; no PharmD group n = 25).
[b]n = 42 (PharmD group n = 34; no PharmD group n = 58).

Table 3. Multivariate Linear Regression for Door-to-Needle (DTN) Time.

Factor	B Coefficient	*P*	95% Confidence Interval
Weekend presentation	−7.80	0.31	−22.94 to 7.34
Daytime presentation	−10.64	0.14	− 24.79 to 3.60
Year	−2.02	0.35	−6.32 to 2.28
PharmD at bedside	−23.5	<0.01	−35.58 to –8.50

≤60 minutes, exceeding the Target: Stroke interventions by nearly 30%.

Pharmacist participation and interventions in emergencies have been associated with a benefit in a variety of clinical settings. One study demonstrated that emergency medicine pharmacist presence decreased diagnosis-to-cardiac catheterization time and door-to-balloon time in ST-segment elevation myocardial infarction.[12] Furthermore, pharmacist presence has demonstrated a decrease in time to and selection of appropriate postintubation sedation.[13] Two recent studies have also demonstrated a similar benefit in DTN time in acute ischemic stroke.[14,15] The first was a retrospective cohort of 105 patients, of which 67 (63.8%) had a pharmacist present. Median DTN time was 69.5 minutes in the pharmacist group compared to 89.5 minutes without a pharmacist ($P < 0.01$). This study demonstrated a nonsignificant increase in DTN goal ≤60 minutes attainment (29.9% PharmD group vs 15.8% no PharmD group, $P = 0.11$).[14] The second study included 97 patients, of which 38 (39.2%) had a pharmacist at the bedside, and found a decrease in DTN time (54 minutes PharmD vs 74 minutes no PharmD, $P = 0.004$) and DTN goal ≤60-minute attainment (71% PharmD vs 38% no PharmD, $P < 0.01$) in the pharmacist group.[15] Our study is the largest to date to explore the impact of pharmacist presence in acute ischemic stroke and differs from prior studies in that this benefit was observed in patients in the ED and admitted to the hospital. Additionally, we adjusted for confounding factors, such as differences in daytime and weekday presentation, via multivariate linear regression. Finally, this is the first study to demonstrate a significant reduction in ITN time with pharmacist presence. This is an important component of DTN time where much of the treatment plan, blood pressure management and patient and family education and dosing, reconstituting, and administering rtPA occurs simultaneously. Pharmacist can expedite ITN time by performing these tasks with the neurology service and nursing staff.

This study is limited by several factors. The single center, retrospective design, and limited number of pharmacists who provide bedside stroke team response at our institution may limit the generalizability of this study. Off-hour and weekend presentation has been identified as a predictor of higher short-term mortality.[16-18] Our no PharmD group had a significantly higher percentage of patients who presented on the weekend or overnight. This was not a significantly correlated with DTN time in our linear regression, but we are unable to control for the contribution of presentation time on the absolute

difference in DTN time observed between groups. Inconsistencies were also found in the year of presentation. Over the course of the study period, more education and interdisciplinary quality improvement measures targeted reducing DTN times. In our study, in 2011, pharmacists actually seemed to increase DTN times compared to other years. We attempted to control for this in the multivariable linear regression. Also, our study does not include any variables which control for performance improvement over time or the training and experience of other members of the stroke team. Additionally, we were unable to collect data such as laboratory testing turnaround time that might have contributed to delays in DTN time. We did not assess the appropriateness of rtPA after administration, which may confound our results. Finally, while our study showed a dramatic decrease in DTN and ITN times with the presence of a pharmacist, it was underpowered to demonstrate differences in ICU or hospital LOS, NIHSS, or mRS score. The influence of pharmacist presence on patient outcomes may be clarified by a larger, multicenter trial.

Conclusion

A pharmacist at the bedside of emergency department or inpatient stroke codes reduced DTN time by 23.5 minutes after accounting for confounders and increased absolute percentage of patients meeting AHA/ASA DTN goal time by 49%. These findings support the inclusion of a stroke-competent pharmacist in the bedside response team for acute ischemic stroke patients.

Authors' Note

The results presented in this article have not been published previously in whole or part, except at the 2016 Society of Critical Care Medicine Congress in Orlando, Florida.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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