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Emergency Medicine Pharmacist Impact on Door-to-Needle Time in Patients With Acute Ischemic Stroke

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Abstract

Background and Purpose: Decreased door-to-needle (DTN) time with tissue plasminogen activator (tPA) for acute ischemic stroke is associated with improved patient outcomes. Emergency medicine pharmacists (EMPs) can expedite the administration of tPA by assessing patients for contraindications, preparing, and administering tPA. The purpose of this study was to determine the impact of EMPs on DTN times and clinical outcomes in patients with acute ischemic stroke who receive tPA in the emergency department. **Methods:** A retrospective, single-center, cohort study of patients who received tPA between August 1, 2012, and August 30, 2014, was conducted to compare DTN times with or without EMP involvement in stroke care. Secondary outcomes included changes in neurological status as measured by the National Institutes of Health Stroke Scale (NIHSS), length of hospital stay, discharge disposition, symptomatic intracranial hemorrhage, and in-hospital all-cause mortality. **Results:** A total of 100 patients were included. The EMPs were involved in the care of 49 patients. The EMP involvement was associated with a significant improvement in DTN time (median 46 [interquartile range IQR: 34.5-67] vs 58 [IQR: 45-79] minutes; $P = .019$) and with receiving tPA within 45 minutes of arrival (49% vs 25%, odds ratio [OR]: 2.81 [95% confidence interval [CI]: 1.21-6.52]). National Institutes of Health Stroke Scale scores were significantly improved at 24 hours post-tPA in favor of the EMP group (median NIHSS 1 [IQR: 0-4] vs 2 [IQR: 1-9.25]; $P = .047$). **Conclusions:** The EMP involvement in initial stroke care was associated with a significant improvement in DTN time.

Keywords

stroke, tissue plasminogen activator, door-to-needle time, emergency medicine, pharmacists

Introduction

Stroke is the fifth leading cause of death and the leading cause of disability in the United States.[1] Tissue plasminogen activator (tPA) is the drug of choice for the treatment of acute ischemic stroke.[2] The benefit of tPA in acute ischemic stroke is time dependent, as earlier administration from the time of onset of symptoms is associated with improved outcomes, while delayed administration results in increased risk of harm.[3,4] The American Heart Association and American Stroke Association (AHA/ASA) guidelines recommend tPA be administered within 60 minutes of arrival to the hospital.[2] An analysis of patients in the Get With the Guidelines national registry between 2003 and 2009 found that only one-quarter (26.6%) of patients received thrombolytics in less than 60 minutes of emergency department (ED) arrival.[5] As a result, the AHA/ASA Target: Stroke Initiative put forth 10 specific recommendations for reducing door-to-needle (DTN) times and improving the care of patients with acute ischemic stroke.[6] These recommendations include advanced notification to the receiving hospital by emergency medical services (EMS), a single-call activation system for a stroke team, and rapid brain imaging. This initiative also recommends ready access to and early preparation of tPA as soon as the patient is considered a possible candidate.

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The emergency medicine pharmacist (EMP) is well suited to serve as a member of a multidisciplinary stroke team. Clinical pharmacists, including EMPs, have an in-depth knowledge of medication therapy, drug interactions and contraindications, pharmaceutical compounding, and intravenous (IV) compatibilities, all of which can be helpful in expediting medication therapy in emergency situations.[7] The purpose of this study was to determine the impact of an EMP on DTN time and clinical outcomes in patients with acute ischemic stroke who receive tPA in the ED.

Methods

Study Design and Setting

This retrospective cohort study was conducted at a 350-bed community teaching hospital which is a Joint Commission–certified primary stroke center with approximately 70 000 ED visits annually. The hospital utilizes the best practice strategies outlined in the Target: Stroke Initiative along with a multidisciplinary stroke team including a neurologist, neurohospitalist physician assistant, a dedicated neurology nurse, ED physician, and an EMP, when available.[6] The ED is staffed with 2 full-time EMPs providing an average of 10 hours of daily coverage, 7 days per week. This study was approved by the local institutional review board and a waiver of informed consent was granted.

Stroke Team Activation Process

When a patient with suspected stroke is identified by EMS, a prearrival alert is called to the ED who then activates the stroke team via a text paging system. Similarly, if a patient arrives through the front door with stroke-like symptoms, the ED will alert the stroke team of his or her arrival. Patients presenting via EMS or through the front door with stroke-like symptoms are taken immediately to the ED computed tomography (CT) scanner for a noncontrast head CT unless they are clinically unstable. If available, the on-call vascular neurologist, neurology physician assistant, and rapid response nurse will all present to the ED CT scanner to assist with patient evaluation and treatment in response to a stroke team alert page.

When an EMP is available, after receiving the stroke team alert page, they will obtain tPA and meet the patient and stroke team members in the ED CT scanner bay. The EMP will interview patients and family members and review available medication histories to assist in identifying medication-related contraindications to tPA. The EMP also assists in verifying that the patient's blood glucose and blood pressure are within recommended ranges prior to initiation of tPA. For patients taking warfarin, the EMP also verifies that the international normalized ratio (INR) is 1.7 or less prior to tPA initiation. The EMP will mix, dose, and administer tPA if indicated and can also dose and administer medications for blood pressure control and symptom management. If the decision is made to administer tPA, the EMP will assist the ED physician or neurologist in educating the patients and family members regarding risk and benefits. When an EMP is not available, the ED charge nurse will obtain tPA from the automated dispensing cabinet and meet the patient in the ED CT scanner and assist with mixing and administering tPA if needed.

Selection of Patients

Study patients were identified retrospectively via an electronic report of all tPA orders between the dates of August 1, 2012, and August 31, 2014. Patients were included if they received tPA for a preliminary diagnosis of acute ischemic stroke in the ED. Patients were excluded if they received tPA at an outside facility prior to being transferred to the study setting, developed stroke symptoms after ED arrival, or tPA was administered for another indication or via the intra-arterial route only. Consecutive patients were enrolled until a number sufficient to fulfill the a priori power threshold (90%) was met. Electronic medical records were reviewed for eligibility, group allocation, and data collection purposes.

Outcomes

The primary outcome of this study was to compare the DTN time between 2 cohorts: (1) in which EMPs were involved in initial stroke care ("EMP group") and (2) where no EMP was present ("no EMP group"). Emergency department documentation, tPA orders, and a chart access summary tool were reviewed in the medical record to determine group allocation. Group allocation was independently verified by a second investigator. The proportion of patients with a DTN time of less than or equal to both 45 and 60 minutes were also calculated and analyzed. Secondary outcomes included measurement of neurological and functional status using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS), which were collected prior to administration of tPA, at 24 hours post-tPA, on the day of hospital discharge, and at a follow-up outpatient visit at least 30 days posthospitalization. Other secondary outcomes included rates of in-hospital all-cause mortality, symptomatic intracranial hemorrhage (sICH), length of hospital stay, discharge disposition (ie, location/setting), and tPA administration errors. Symptomatic intracranial hemorrhage was defined as evidence of hemorrhage on follow-up CT scan or magnetic resonance imaging (MRI) within 36 hours of tPA administration and provider documentation of worsening neurological status attributed to hemorrhage. Prior to hospital discharge, patients were diagnosed with MRI-confirmed stroke, MRI-negative stroke, or a stroke mimic. The MRI-confirmed stroke was defined as evidence of acute cerebral infarct on follow-up MRI. The MRI-negative stroke was defined as a negative follow-up MRI, but stroke was believed to be the most likely diagnosis as documented by the physician. Stroke mimic was defined as a diagnosis other than stroke that was believed to be

responsible for the presenting symptoms in addition to a negative MRI (eg, complex migraine).

Analysis

Statistical analyses were performed using SPSS version 22 (SPSS Inc, Chicago, Illinois). We calculated that 100 patients would be needed to detect a 30% difference in DTN time between groups with 90% power and a 2-sided α of .05. This difference was based on the institution's known baseline DTN times prior to the study period. The median DTN time in 2011 was 83 minutes, and therefore a 30% decrease would be required to meet the AHA/ASA-recommended DTN goal of less than or equal to 60 minutes. Nominal variables were assessed using a χ^2or Fisher exact test as appropriate. Ordinal or nonparametric continuous data were assessed using a Mann-Whitney *U* test, while parametric continuous data were assessed via the Student *t* test. A post hoc multivariate logistic regression was performed to assess for factors that independently contributed to the likelihood of a DTN time of less than or equal to 45 minutes.

Results

Study Participants

A total of 114 patients were reviewed to obtain 100 eligible patients between August 1, 2012, and August 31, 2014. Of the excluded patients, 3 were excluded due to the administration of tPA at an outside medical facility, 6 due to the onset of stroke symptoms while the patient was already hospitalized, and 5 due to receipt of only intra-arterial tPA. Baseline characteristics are summarized in Table 1. There were a significantly higher proportion of patients with a past medical history of hypertension in the no EMP group; however, the number of patients who required IV antihypertensive prior to receiving tPA was not different between groups. The majority of patients in both groups arrived to the ED via EMS and had similar times from last known well. Although all patients had to have a preliminary diagnosis of acute ischemic stroke to be eligible for inclusion, the diagnosis may have subsequently changed during the hospital stay. There were a significantly higher proportion of patients in the no EMP group who had MRI-confirmed stroke, although the number of patients in each group who were diagnosed with stroke mimics was the same.

Table 1. Patient Demographics and Clinical Characteristics.

Variable	EMP (n = 49)	No EMP (n = 51)
Mean (SD) age, years	69.0 (14.9)	69.8 (16.0)
Mean (S.D) weight, kg	88.8 (21.8)	84.8 (33.9)
Male, no. (%)	27 (55)	20 (39)
Race/ethnicity, no. (%)		
Caucasian	41 (84)	41 (80)
African American	4 (8)	7 (14)
Hispanic	2 (4)	2 (4)
Unknown/declined	2 (4)	0 (0)
Asian	0 (0)	1 (2)
Comorbidities, no. (%)		
Hypertension[a]	33 (67)	45 (88)
Hyperlipidemia	31 (63)	30 (59)
Obesity (BMI ≥ 30)	20 (41)	19 (37)
Diabetes mellitus	15 (31)	14 (27)
Smoking history	14 (29)	13 (25)
Previous MI or CAD	12 (24)	12 (24)
Previous stroke/TIA	10 (20)	15 (29)
Atrial fibrillation	9 (18)	12 (24)
History of migraine headache	4 (8)	6 (12)
Peripheral vascular disease	1 (2)	3 (6)
Home medications, no. (%)		
Aspirin	24 (49)	24 (47)
Thienopyridine	6 (12)	4 (8)
Warfarin	1 (2)	6 (12)
Method of arrival to ED, no. (%)		
EMS	35 (71)	34 (67)
Private automobile	14 (29)	17 (33)
Median (IQR) last known well to ED presentation, minutes	90 (57-115)	78 (49-109)
Mean (SD) systolic blood pressure,[b] mm Hg	151 (23)	153 (24)
Mean (SD) diastolic blood pressure,[b] mm Hg	77 (17)	78 (17)
Need for IV antihypertensives prior to tPA, no. (%)	11 (22)	13 (25)
Diagnosis prior to hospital discharge, no. (%)		
MRI-confirmed stroke[a]	22 (45)	35 (69)
MRI-negative stroke[a]	24 (49)	13 (25)
Stroke mimic	3 (6)	3 (6)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; ED, emergency department; EMP, emergency medicine pharmacist; EMS, emergency medical services; IQR, interquartile range; IV, intravenous; MI, myocardial infarction; MRI, magnetic resonance imaging; SD, standard deviation; TIA, transient ischemic attack; tPA, tissue plasminogen activator.
[a]$P \leq .05$.
[b]Prior to administration of tPA.

Main Results

Patients in the EMP group had significantly shorter DTN times compared to the no EMP group (Table 2). A difference in median DTN time of 12 minutes in favor of the EMP group was observed (46 [34.5-67] vs 58 [45-79] minutes; $P = .019$). There was no statistically significant difference in the proportion of patients who received tPA within 60 minutes between groups (71% vs 61%, odds ratio [OR]: 1.61 [95% confidence interval [CI]: 0.70-3.72]). There were a significantly higher proportion of patients in the EMP group who received tPA within 45 minutes of presentation to the ED (49% vs 25%, OR: 2.81 [95% CI: 1.21-6.52]). Multivariate logistic regression showed that involvement of an EMP was independently associated with an increased likelihood of receiving tPA within 45 minutes of arrival to the ED. Additionally, arrival

Table 2. Median Door-to-Needle Time and Proportion of Patients Meeting Door-to-Needle Goals.

Variable	EMP (n = 49)	No EMP (n = 51)	P
Median (IQR) DTN time, minutes	46 (34.5-67)	58 (45-79)	.019
DTN ≤ 45 minutes, no. (%)	24 (49)	13 (25)	.015
DTN ≤ 60 minutes, no. (%)	35 (71)	31 (61)	.261

Abbreviations: DTN, door-to-needle; EMP, emergency medicine pharmacist; IQR, interquartile range.

Table 3. Multivariate Logistical Regression Analysis of Factors That Predict a Door-to-Needle Time of Less Than 45 minutes.

Variable	Odds Ratio (95% CI)
EMP involvement in stroke care	1.26 (1.05-1.50)
Arrival by EMS	1.36 (1.12-1.66)
tPA prepared in ED	1.22 (1.02-1.46)
Requirement of antihypertensives prior to tPA	0.88 (0.71-1.08)

Abbreviations: CI, confidence interval; ED, emergency department; EMP, emergency medicine pharmacist; EMS, emergency medical services; tPA, tissue plasminogen activator.

Table 4. Median National Institutes of Health Stroke Scale Scores at Baseline and Post-tPA.

Variable	EMP	No EMP	P
Prior to tPA			.180
Median (IQR)	5 (3-8.5)	6 (4-13)	
n	45	48	
24-Hour post-tPA			.047
Median (IQR)	1 (0-4)	2 (1-9.25)	
n	43	46	
At discharge			.077
Median (IQR)	0 (0-4)	2 (0-6)	
n	44	43	
At follow-up visit			.198
Median (IQR)	0 (0-2)	1 (0-5.5)	
n	15	13	
Days to follow-up			
Median (IQR)	53 (36-91)	58 (23-77.5)	.705

Abbreviations: EMP, emergency medicine pharmacist; IQR, interquartile range; tPA, tissue plasminogen activator.

by EMS and mixing of tPA in the ED were predictive of a DTN time of less than or equal to 45 minutes (Table 3). The need for IV antihypertensives was not associated with a delay in tPA administration in either group.

Baseline NIHSS scores were similar between groups (Table 4). There was a significant difference in median NIHSS scores at 24 hours post-tPA in favor of the EMP group (1 [IQR: 0-4] vs 2 [IQR: 1-9.25]; $P = .047$). Five patients experienced sICH, 3 in the EMP group and 2 in the no EMP group ($P = .678$); 3 of these patients expired. One patient who experienced sICH and subsequently expired was taking warfarin prior to hospital arrival; however, the patient's INR was less than 1.8 at the time of tPA administration. There was no difference between groups in length of hospital stay (median stay 2.6 [IQR: 1.8-3.9] vs 2.9 [IQR: 2.0-4.0] days; $P = .500$) or proportion of patients discharged to home (30 [65%] vs 26 [54%]; $P = .384$).

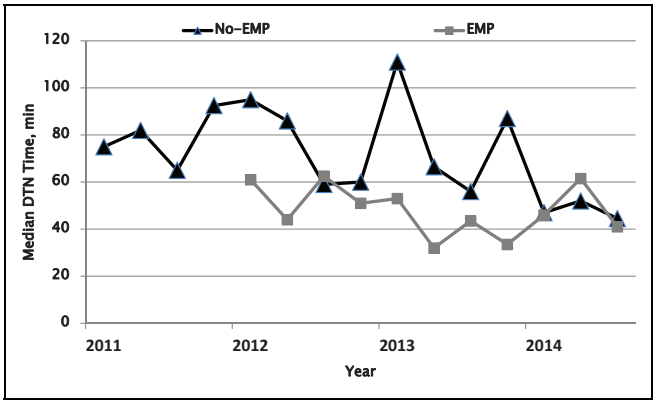

Figure 1. Quarterly median door-to-needle times before and during the study period. EMP indicates emergency medicine pharmacist; DTN, door to needle.

There were no medication errors in the EMP group and 2 errors in the no EMP group ($P = .495$). One of these errors resulted from tPA being mixed incorrectly which led to a delay in therapy. The other error occurred due to an incorrectly calculated infusion of tPA being administered to the patient.

Discussion

The AHA/ASA guidelines focus on improving stroke care with an emphasis on developing strategies to reduce DTN times.[2] Our study demonstrated that EMP involvement in stroke care for patients receiving tPA improved DTN times and was significantly associated with receiving tPA in less than 45 minutes from arrival. Previous research has demonstrated the beneficial impact of the EMP on patient care in the ED and resuscitation settings, including improved adherence to advanced cardiac life support guidelines, decreased door-to-catheterization and door-to-balloon times for acute myocardial infarction, and improved safety through decreased medication errors.[8-10] In patients with acute ischemic stroke, the EMP can participate in assessing for contraindications to thrombolytic therapy, drug procurement, preparation, and administration, and blood pressure management. Previous studies have specifically addressed the impact that EMPs can have on this population. Gosser et al found that the participation of an EMP in initial stroke care improved the median DTN time by 20 minutes ($P = .0027$).[11] Similarly, Montgomery et al found that the proportion of patients who received tPA within 45 minutes more than doubled when an EMP was present (42% vs 19%; $P = .012$).[12] As was noted in our study, there were 2 errors related to tPA dose calculation and

preparation. These errors may be avoided by EMP participation in care.

We observed a median 12-minute decrease in DTN time when an EMP was involved in the administration of tPA. This effect appeared to be consistent throughout the study period (Figure 1). A multicenter study examining the difference in DTN times and outcomes before and after implementation of process improvement strategies outlined in phase I of Target: Stroke found that median DTN time decreased from 77 to 67 minutes.[13] This 10-minute decrease was associated with significant improvements in in-hospital all-cause mortality, sICH, and the proportion of patients discharged to home. The authors of this study concluded that an improvement in DTN time of as little as 10 minutes could have a significant impact on the efficacy and safety of treatment with tPA. In our study, we observed a statistically significant difference in NIHSS scores in favor of the EMP group 24 hours post-tPA. There was a numerical difference in NIHSS scores at the time of discharge and at a follow-up visit; however, this difference was not statistically significant. Other secondary outcomes, including in-hospital all-cause mortality, length of hospital stay, and discharge disposition were similar between groups. We also observed a 5% rate of sICH, which is comparable to previously published literature.[3,4,13]

In October 2014, the AHA/ASA released the campaign manual for phase II of Target: Stroke that focuses on improvement in stroke care primarily through developing strategies to reduce DTN times, thereby increasing the number of eligible patients who receive tPA within 60 minutes of hospital arrival.[14] Phase II of Target: Stroke increases the goal for the proportion of patients who receive tPA within 60 minutes from 50% (phase I goal) to 75% (phase II goal). Phase II also sets a new target for 50% of eligible patients with stroke to receive tPA within 45 minutes.[14] Several measures have been recommended to reduce DTN for patients with acute ischemic stroke.[13,15] In this study, multivariate logistic regression found that EMP involvement in stroke care along with arrival by EMS and tPA prepared in the ED were independently associated with a DTN of less than 45 minutes.

There are a few limitations to note within this study. First, the accuracy of the data is limited to the completeness of documentation by hospital staff as is inherent in retrospective studies. Therefore, specific causes of prolonged DTN times are difficult to identify. Our planned data collection and analysis included a comparison of mRS scores at various time points during hospitalization and at a follow-up visit; however, less than half of the patients had documented baseline scores, therefore, we were unable to compare patient functionality between groups. Other secondary outcomes, including in-hospital all-cause mortality, length of hospital stay, and discharge disposition were similar between groups. Although previous literature has demonstrated differences in these outcomes with timely tPA administration, this study was likely underpowered to detect a difference. We did note a significant difference in NIHSS scores at 24 hours post-tPA in favor of the EMP group; however, this group also had a higher proportion of MRI-negative stroke. Next, patients included in the EMP group were inherently more likely to be seen in the afternoon or evening hours, which corresponds to the hours of clinical pharmacy service coverage. It is possible that patients in both groups may have experienced differences in available resources with regard to nursing, radiology, and in-house neurology evaluation. This difference in resource availability was somewhat alleviated during the study period in 2012, when ED charge nurses were trained to mix tPA in the ED when an EMP was not present; prior to this time, tPA was prepared and sent from the central pharmacy. Finally, at our study site, EMPs may administer tPA and other medications which may further expedite therapy in these patients. However, we were unable to track the frequency of tPA administered by an EMP versus non-EMP, and thus the impact of this on our results is unclear.

Conclusion

The involvement of an EMP in the care of patients with acute ischemic stroke was associated with a significant decrease in DTN time and independently associated with a DTN of less than 45 minutes. This finding supports the inclusion of an EMP in the care of patients with ischemic stroke in the ED.

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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