

ORIGINAL RESEARCH

**THE EFFECT OF tPA ON IN-HOSPITAL MORTALITY
IN PATIENTS HOSPITALIZED WITH ISCHEMIC
STROKE IN FLORIDA FROM 2008-2012**

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ABSTRACT

Introduction. In the U.S., tissue Plasminogen Activator (tPA) is the only approved thrombolytic drug to re-canalize occluded arteries in patients with acute ischemic stroke (AIS). With timely administration, tPA may improve the patient prognosis. The percentage of AIS patients that receive tPA in the U.S., however, varies from 3.0% to 8.5%. Further, there is scarce information on the impact of tPA and short-term mortality among Floridians hospitalized with AIS. This study investigates factors associated with in-hospital mortality among patients admitted to Florida hospitals with AIS who received tPA compared to those who did not receive the thrombolytic.

Methods. This is a secondary analysis of the Florida Stroke Registry for 2008-2012. We assessed the association between tPA administration and in-hospital mortality utilizing logistic regression to estimate unadjusted and adjusted odds ratios. Pearson correlation coefficients were used to diagnose for collinearity.

Results. A total of 133,052 ischemic stroke patients (51.9% women, average age 71.7±14.4 years) comprised our study sample. Approximately 5% (6,357) of AIS patients received tPA. After adjusting for potential confounders, AIS patients who received tPA were twice as likely to die than AIS patients not receiving tPA (OR=2.0; 95% CI= 1.8-2.2). AIS patients 90 years or older were five times more likely to die than AIS patient < 60 years (OR=5.0; 95% CI 4.4-5.7). Women were less likely to die compared to men (OR=0.9; 95% CI=0.87-0.99). Factors significantly increasing the likelihood of in-hospital mortality among AIS patients receiving tPA included being admitted to teaching hospitals (OR=1.6, 95% CI=1.5-1.7), lack of health insurance coverage (OR=2.0, 95% CI=1.8-2.3), extended hospitalization length of stay > 6 days (OR=1.2, 95% CI= 1.1-1.2), and not being assigned emergent priority at admission (OR=2.7, 95% CI= 2.5-2.9).

Conclusion. Our findings suggest that the likelihood of in-hospital mortality among Floridian patients with AIS is twice as higher among those receiving tPA than those AIS patients not receiving the thrombolytic. Increasing age, being a man and admitted to a teaching hospital, lack of health insurance, extended length of stay, and not receiving emergent priority at admission also increased the likelihood of in-hospital dead for AIS patients after receiving tPA.

KEYWORDS: t-PA; tpa; Ischemic Stroke; Hospital Mortality; Florida; USA

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INTRODUCTION

Stroke is one of the most common causes of disability and is considered the fifth leading cause of death in the U.S. It is estimated there are 795,000 new cases of stroke each year in the U.S. [1]. For acute ischemic stroke (AIS), thrombolytic re-canalization of an occluded artery may reduce complications of injury to the brain if it is done before the infarction is complete. It is currently considered to be the best form of treatment in order to

give patients the best chance of recovering normal function [2-3]. Tissue Plasminogen Activator (tPA), approved by the FDA in 1996, is currently the only thrombolytic re-canalization therapy available. Since its approval, the use of tPA has improved the outcome of AIS among certain patients [4].

Studies conducted in the U.S. estimate that between 3.0% and 8.5% of the patients with an AIS have received tPA [5]. Many studies have examined the associations

between tPA and other outcomes, but only a small number of studies outside of clinical trials have examined in-hospital mortality as an outcome [6-9]. No such studies have been conducted in Florida. This study aims to investigate the association between tPA administration and in-hospital mortality among patients hospitalized with AIS in Florida.

METHODS

Study Design and Population

This is a secondary analysis of data collected by the Florida Agency for Health Care Administration (AHCA), which has a non-concurrent prospective study design. This study includes patients 18 years old and older with a discharge diagnosis of acute ischemic stroke (International Classification of Diseases 9th Revision (ICD-9) codes 434.00 to 434.91) from Florida acute care hospitals between 2008 and 2012. Patients with diagnoses of transient ischemic attack (ICD-9 code 435), head trauma (ICD-9 codes 959.0, 800-804, 850-854), epidural hematoma, subdural hematoma, subarachnoid hemorrhage (ICD-9 code 852) and those patients for which an External Cause of Injury Code is reported were excluded from analysis.

Data Source

The database consists of hospital discharge data reported to Florida AHCA, which is collected on a quarterly basis and includes approximately 2.5 million records per year. To protect patient privacy, prior to releasing the data personal identifiers are removed, changing dates of birth to ages, discharge dates to quarters of calendar years, and procedure dates to number of days to procedure. Additionally, AHCA does not report patient ID numbers, names or social security numbers.

Variables

The initial sample size was 333,366 records over the study years. Categories of information analyzed included demographic characteristics, such as age, gender, race, and insurance status, as well as other clinical characteristics such as teaching status of the hospital, length of stay, admission priority, stroke center designation, location of the hospital, and whether or not the patient received tPA. All of these were categorized based on previous, similar studies [7,10-11]. Age was categorized as follows: less than 60 years, 60-69, 70-79, 80-89, and 90 years or older. Race was categorized as white, black, and other (which included American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and others). Ethnicity was categorized as Hispanic and non-Hispanic. Patients with any type of insurance were categorized as having insurance. Self-pay patients and patients without insurance were categorized as uninsured/self-payment. Admission priority was classified as emergent or non-emergent cases. Stroke center designation was defined as having stroke center designation at any time between 2008 to 2012 and it was expressed as a dichotomous variable. Length of stay was categorized as up to five days or more than five days. Location of hospital was categorized as rural or other (which included general hospital, psychiatric hospital, intermediate residential treatment facility, rehabilitation hospital, special medical hospital and hospital excluding obstetrics).

Statistical Methods

The chi-square test was used to examine the association between categorical variables. Variables conservatively associated with both tPA administration and in-hospital mortality (p-value ≤ 0.1) were included in the adjusted

logistic regression model as potential confounders. Factors that did not meet this criteria were included in the adjusted model if deemed clinically important. Binary logistic regression was utilized to estimate unadjusted and adjusted odds ratios. A p-value of .05 and a 95% confidence interval was used to assess significance of the odds ratios. Collinearity was assessed using Pearson correlation coefficients. All data were analyzed using SPSS version 22 (IBM).

RESULTS

The final number of patients with acute ischemic stroke was 133,052 patients. Approximately 5% (3,134 men and 3,223 women) received tPA. In-hospital mortality was higher among AIS patients receiving tPA (6.7%), as compared to those AIS patient not treated with tPA (3.7%; $p < .001$). The majority (68%) of AIS patients receiving tPA were admitted to non-teaching hospitals, and had lower in-hospital mortality (3.5%) as compared to teaching hospitals (4.9%; $p < 0.001$). Eight out of ten patients who received tPA were white. A significant higher proportion of white patients received tPA (80.1% vs. 75.4%) contrary to a lower proportion of blacks or African Americans and other races who received less tPA (80.1% vs. 19.6% and 4.7% vs. 5.0%, respectively). Only 7% of AIS patients received tPA when admitted with non-emergent status, and were three times more likely to die than those receiving admission priority as emergent (OR=2.7; 95% CI=2.5-2.9).

Table 1 describes demographic and clinical characteristics of adult ischemic stroke patients hospitalized in Florida State from 2008 to 2012 according to the administration of tPA.

TABLE 1: Characteristics of adult ischemic stroke patients in Florida, 2008-2012 (N=133,052)

Patient Characteristics	tPA administration		P-value
	No N (%)	Yes N (%)	
Age (years)			<.001
< 60	26813 (21.2)	1383 (21.7)	
60-69	24744 (19.5)	1207 (19.0)	
70-79	30200 (23.8)	1644 (25.9)	
80-89	34102 (26.9)	1681 (26.4)	
≥ 90	10836 (8.6)	444 (7.0)	
Gender			.4
Men	60824 (48.0)	3134 (49.3)	
Women	65871 (52.0)	3223 (50.7)	
Race			<.001
White	94897 (75.4)	5048 (80.1)	
Black or African American	24675 (19.6)	953 (15.1)	
Other*	6247 (5.0)	298 (4.7)	
Ethnicity			<.001
Hispanic	12083 (12.0)	517 (9.8)	
Non-Hispanic	88845 (88.0)	4734 (90.2)	
Teaching Status			<.001
Teaching hospital	33580 (26.5)	2066 (32.5)	
Non-teaching hospital	93115 (73.5)	4291 (67.5)	
Length of Stay			<.001
Less than 6 days	88607 (69.9)	3674 (57.8)	
6 days or more	38088 (30.1)	2683 (42.2)	
Insurance Status			.09
Has Insurance	116988 (92.3)	5907 (92.9)	
Uninsured/Self-payment	9707 (7.7)	450 (7.1)	
Admission Priority			<.001
Emergent	90429 (88.5)	4953 (93.0)	
Non-emergent	11707 (11.5)	371 (7.0)	
Stroke Center Designation at any Time, 2008-2012			.005
No	44435 (43.5)	2420 (45.5)	
Yes	57698 (56.5)	2904 (54.5)	
Location of Hospital			<.001
Other	123965 (97.9)	6313 (99.4)	
Rural	2706 (2.1)	40 (0.6)	

*Other race includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and others/unspecified.

The proportion of patients in the <60 years-old bracket who received tPA was slightly higher than those not receiving tPA. Conversely, the proportion of patients >90 years-old who received tPA was significantly lower than those not receiving tPA. The higher proportion of patients receiving tPA was observed in the 70-79 year-old and in the 80-89 year-old brackets. The proportion of whites

who received tPA was approximately 5% higher than whites not receiving tPA. However, the proportion of blacks or African Americans and patients classified as "other" races, as well as Hispanics patients who received tPA was significantly lower than their counterparts who did not receive tPA. The proportion of patients hospitalized in teaching hospitals as well as those who received a priority admission code was significantly higher than those patients not receiving tPA. Overall, the proportion of patients staying 6 days or more was approximately 12% higher among those receiving tPA. The proportion of patients who received tPA was significantly lower in hospitals who had a Stroke Center designation at any time between 2008 and 2012, and in rural hospitals. Similar distribution of patients receiving or not receiving tPA was observed between gender and insurance status.

Table 2 describes the bivariate associations between in-hospital mortality and tPA administration, as well as other possible confounders, among adult patients with ischemic stroke in Florida from 2008 to 2012.

TABLE 2: Bivariate associations between in-hospital mortality, tPA administration, and other patient characteristics among adult patients with acute ischemic stroke in Florida, 2008-2012 (N=133,052)

Patient Characteristics	In-Hospital Mortality		P-value
	Alive N (%)	Dead N (%)	
tPA Administration			<.001
No	121923 (96.3)	4729 (3.7)	
Yes	5930 (93.3)	423 (6.7)	
Age (years)			<.001
< 60	27585(98.0)	576 (2.0)	
60-69	25211 (97.2)	732 (2.8)	
70-79	30681 (96.4)	1158 (3.6)	
80-89	33929 (94.8)	1853 (5.2)	
≥90	10447 (92.6)	833 (7.4)	
Gender			.001
Men	61559 (96.3)	2357 (3.7)	
Women	6294 (96.0)	2795 (4.0)	
Race			<.001
White	95831 (95.9)	4095 (4.1)	
Black or African American	24852 (97.1)	755 (2.9)	
Other ^a	6291 (96.2)	250 (3.8)	
Ethnicity			.001
Hispanic	12046 (95.6)	550 (4.4)	
Non-Hispanic	90023 (96.2)	3517(3.8)	
Teaching Status			<.001
Teaching hospital	33880 (95.1)	1733 (4.9)	
Non-teaching hospital	93973 (96.5)	3419 (3.5)	
Length of Stay			<.001
Less than 6 days	88846 (96.3)	3399 (3.7)	
6 days or more	39007 (95.7)	1753 (4.3)	
Insurance Status			.06
Has Insurance	118125 (96.2)	4724 (3.8)	
Uninsured/ Self-Payment	9728 (95.8)	428 (4.2)	
Admission Priority			<.001
Emergent	92225 (96.7)	3121 (3.3)	
Non-emergent	11055 (91.6)	1009 (8.4)	
Stroke Center Designation at Any Time, 2008-2012			<.001
No	44919 (95.9)	1927 (4.1)	
Yes	58361 (96.4)	2203 (3.6)	
Location of hospital			.15
Other	125172 (96.1)	5059 (3.9)	
Rural	2654 (96.6)	92 (3.4)	

^aOther race includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and others/unspecified.

The proportion of patients who died and received tPA was 1.8 times higher than those who did not received tPA. The proportion of patients dying in the hospital who were 90 years of age or older was 3.7 time higher than those in the youngest group (<60 years old). The proportion of women who died in the hospital was significantly higher than men. The proportion of white patients who died in the hospital was significantly higher than blacks or than patients classified as in "other" races. The proportion of patients admitted to teaching hospitals or with a Stroke Center designation at any time during the study period, and those with non-emergent priority admission was significantly higher than their counterpart patients admitted to a non-teaching hospital, to hospitals without a Stroke Center designation, and to a teaching hospital, respectively. The proportion of patients who died in the hospital was significantly higher among those staying 6 or more days. Similar proportions of in-hospital

deaths were observed according to insurance status and hospital location. No collinearity was found between independent variables included in the adjusted model.

Table 3 describes the unadjusted and adjusted odds ratios of in-hospital mortality in adult patients hospitalized with an acute ischemic stroke in Florida from 2008 to 2012.

TABLE 3: Adjusted and unadjusted associations between in-hospital mortality, tPA administration, and other patient characteristics among adult patients with acute ischemic stroke in Florida, 2008-2012 (N=133,052)

Patient Characteristics	Unadjusted		Adjusted	
	OR (95% CI)	P-value	OR (95% CI)	P-value
tPA Administration				
No	Ref.		Ref.	
Yes	1.8 (1.7, 2.0)	<.001	2.0 (1.8, 2.2)	<.001
Age				
< 60	Ref.		Ref.	
60-69	1.4 (1.3, 1.6)	<.001	1.6 (1.4, 1.8)	<.001
70-79	1.8 (1.6, 2.0)	<.001	2.2 (1.9, 2.5)	<.001
80-89	2.6 (2.4, 2.9)	<.001	3.2 (2.8, 3.6)	<.001
≥90	3.9 (3.4, 4.3)	<.001	5.0 (4.4, 5.7)	<.001
Gender				
Men	Ref.		Ref.	
Women	1.1 (1.0, 1.2)	<.001	0.93 (0.87, 0.99)	.03
Race				
White	Ref.		Ref.	
Black or African American	0.7 (0.7, 0.8)	<.001	0.95 (0.87, 1.05)	.30
Other ^a	0.9 (0.8, 1.1)	.30	0.9 (0.8, 1.1)	.44
Ethnicity				
Hispanic	1.2 (1.1, 1.3)	<.001	1.08 (0.98, 1.20)	.13
Non-Hispanic	Ref.		Ref.	
Teaching Status				
Teaching hospital	1.4 (1.3, 1.5)	<.001	1.6 (1.5, 1.7)	<.001
Non-teaching hospital	Ref.		Ref.	
Length of Stay				
Less than 6 days	Ref.		Ref.	
6 days or more	1.1 (1.1, 1.2)	<.001	1.2 (1.1, 1.2)	<.001
Insurance Status				
Has Insurance	Ref.		Ref.	
Uninsured/ Self-Payment	1.1 (0.99, 1.22)	.06	2.0 (1.8, 2.3)	<.001
Admission Priority				
Emergent	Ref.		Ref.	
Non-emergent	2.7 (2.5, 2.9)	<.001	2.7 (2.5, 2.9)	<.001
Stroke Center Designation at Any Time, 2008-2012				
No	1.1 (1.1, 1.2)	<.001	1.01 (0.94, 1.08)	.82
Yes	Ref.		Ref.	
Location of Hospital				
Other	Ref.		Ref.	
Rural	0.9 (0.7, 1.1)	.15	1.1 (0.8, 1.3)	.66

^aOther race includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and others/unspecified.

The odds for in-hospital mortality increased slightly from 1.8 to 2.0 times in the unadjusted and adjusted models in patients who received tPA as compared to those who did not received tPA. The adjusted model shows that advanced age increased up to 5 times in patients 90 years of age and older as compared to patients younger than 60 years old. In addition, women had 7% lower odds for in-hospital mortality than men. The odds of dying during hospitalization increased significantly in patients admitted to teaching hospitals from 40% to 60% between the unadjusted and the adjusted models, as compared to patients admitted to non-teaching hospitals. Patients staying 6 or more days in the hospital had 20% higher risk of dying, as compared to those patients staying less than 6 days. Although the unadjusted model shows non-statistical significant differences between insurance status, after adjustment for all possible confounders, uninsured patients and those who self-paid had twice the odds of dying, as compared to patients with any type of insurance. Patients receiving non-emergent admission priority had 2.7 times higher odds of dying as compared to those patients receiving priority of admission. Finally, similar odds of dying during hospitalization after receiving tPA was observed in the adjusted model in whites, blacks and other races, in Hispanics vs. non-Hispanics, in patients hospitalized to centers with a stroke center designation at any time between 2008 and 2012, and among patients admitted to urban or rural hospitals.

DISCUSSION

Outcomes from this study suggest that tPA administration in patients hospitalized with AIS increases the odds of in-hospital death two-fold. One possible reason for this

finding may be due to the cross-sectional nature of the study. Thus, a causal relationship between tPA administration and mortality could not be assessed. In addition, because of the lack of information on stroke severity, it was not possible to determine if patients with a worse prognosis were more likely to receive tPA compared to those who did not.

The findings of this study were similar to one study reported by Katzan et al., which was based on 70 patients treated with intravenous tPA in hospitals located in the Cleveland, Ohio, U.S. area [6]. They found patients receiving tPA had significantly increased odds of in-hospital mortality compared to patients who did not receive it. Reed et al. and Heuschmann et al. found similar results [7-9].

In the unadjusted model, patients who didn't have insurance had similar odds of death compared to patients who had insurance. However, in the adjusted model patients with no insurance had twice the odds of death. This may be because uninsured patients have a higher likelihood of adverse outcomes in general due to poor access to care [12]. Non-emergent cases had three-fold the odds of death compared to emergent cases; this association was the same in both the unadjusted and adjusted models. This finding may be because stroke patients do not always present with signs and symptoms that are recognized as emergent [4]. Patients who were 80-89 years old had an increased OR in the adjusted model (OR=3.2; 95 % CI 2.8-3.6; $p<0.001$) compared to the unadjusted model (OR=2.6; 95

% CI 2.4-2.9; $p<0.001$). Tanne et al. also found older age increased the OR of in-hospital mortality by three fold [10]. These findings may indicate that special attention should be paid to older patients receiving tPA.

A strength of this study is its large sample size, which included 133,052 patients from the Florida population. One limitation of this study is that information related to factors of interest such as severity of illness, comorbidities (hypertension, diabetes, previous stroke, coronary artery disease and hyperlipidemia), time to tPA administration, physician specialty, and smoking was not available through the Florida stroke registry. Additionally, data were only collected from Florida, and the number of patients who received tPA was only 6353 (5.01%). Furthermore, there were missing data in admission priority (19.2%), ethnicity (20.2%) and stroke center designation (19.2%).

While the study results are generalizable to Florida, future studies should include other states and more detailed information related to possible risk factors. A prospective cohort study design may also be helpful to determine whether tPA administration is related to worsening the patient's outcome.

In conclusion, tPA appears to be associated with in-hospital mortality. However, this association might be due to the cross-sectional approach of the secondary data analysis. When treating ischemic stroke patients, health care providers should pay attention to patient's insurance status, age, non-emergent cases, and their hospital's teaching status.

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LIST OF ABBREVIATIONS

AHCA	Agency for Health Care Administration
AIS	Acute Ischemic Stroke
CI	Confidence Interval
ICD-9	International Classification of Diseases, 9th Revision
OR	Odds Ratio
tPA	tissue Plasminogen Activator

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AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals](#) of the [International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

COMPETING INTERESTS

The authors declare no competing interests.

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