Distance From Home to Hospital and Thrombolytic Utilization for Acute Ischemic Stroke

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Treatment of acute stroke with trombolytic therapy has been limited because of the narrow treatment window. Distance from home to hospital may affect arrival time and likelihood of receiving thrombolytic therapy for acute stroke. The present study included stroke subjects seen at Barnes Jewish Hospital in 2006-2007, residing in St Louis City/County, who were at home at the time of the stroke (n = 416). A network distance was calculated by mapping the best route from each subject's home to the hospital on a street network grid. Patients were grouped by distance into quintiles, and the group living the closest (group A, first quintile) was compared with the remainder of the cohort (group B). Outcomes of interest were rate of arrival within 3 hours of stroke onset (timely arrival) and rate of thrombolytic administration. The relative rate (RR) of each outcome was calculated for group A versus group B. A multivariate model of thrombolytic administration was created correcting for potential confounders. There was no difference in timely arrival between groups. The rate of thrombolytic administration was 13/100 for group B and 23/100 for group A, for an RR 0.55 (95% confidence interval [CI], 0.31-0.097) for group B versus group A. In the multivariate model, only National Institutes of Health Stroke Scale score was a significant confounder. The adjusted RR of thrombolytic treatment was 0.59 (95% CI, 0.34-0.99) for group B versus group A. Our data indicate that patients living in close proximity to the hospital are more likely to receive thrombolytic therapy for stroke compared with those living farther away. This finding cannot be explained by earlier arrival time. **Key Words:** Geographic information system—health care delivery—transportation of patients—Prehospital Emergency Care.

Treatment with the thrombolytic agent tissue plasminogen activator (tPA) decreases disability after acute ischemic stroke,[1] but its use has been limited by the narrow time window after stroke onset during which the drug can be administered.[2-5] Clinical trials using intravenous thrombolytic agents outside this window have shown mixed results, with some finding no benefit[6,7] and others suggesting effectiveness for up to 4.5 hours.[8,9] The use of magnetic resonance imaging diffusion/perfusion mismatch to expand the treatment window has shown some promise,[10] but this approach is awaiting validation. Although some have advocated expanding the time window for tPA therapy,[11] current practice in the United States generally is treatment within 3 hours of stroke symptom onset.

Given the short time window available for thrombolytic therapy, programs to expedite the evaluation and

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treatment of stroke patients have been developed. Community hospitals have partnered with regional stroke centers that have expertise in acute stroke management.[12] In addition, public service announcements have improved public awareness of stroke symptoms.[13] Despite these efforts, however, in the United States only 15%-27% of patients arrive at the hospital emergency department (ED) within 3 hours of stroke onset, and only 2%-7% receive tPA therapy for stroke.[2,3]

The degree of neurologic deficit is a key determinant of time of arrival to the ED after stroke onset, with those with more profound deficits arriving earlier than those with milder symptoms.[14] Data on the association between sex, race, and age and time of ED arrival after stroke symptom onset are mixed.[15,16]

Aside from the issue of time, other factors that limit tPA treatment of stroke include older age, resolved or minor stroke symptoms, and severe neurologic deficits.[2-5] Racial and sex inequality also have been studied as a potential factors affecting tPA administration in stroke patients.[17] African Americans are less likely than Caucasians to receive tPA for stroke,[17] and women are less likely than men to receive tPA for stroke.[18] The role of spatial inequality (the distance from home to a hospital) has not been investigated, but could conceivably affect the likelihood of tPA administration for acute stroke given the limited window of opportunity for treatment. This may be true even in urban settings, where 911 and ambulance services are readily available.

In this study we hypothesized that persons living within close proximity to the hospital are more likely to arrive within the 3-hour window, and also are more likely to receive tPA.

Methods

Study Population

This retrospective cohort study used an archival data set originating from the Cognitive Rehabilitation Research Group (CRRG) at Washington University. As part of an Institutional Review Board-approved protocol, the CRRG prospectively collected sociodemographic and medical data on each patient admitted with the diagnosis of stroke to Barnes Jewish Hospital (BJH) in St. Louis MO who consented to participate. During the time frame of this study, the consent rate was 94.67%; 4.2% of patients were not approachable due to their medical condition, 0.82% were missed during the hospital stay, and 0.31% were asked but declined to participate. Data used for this study were limited to those subjects in the CRRG registry with a diagnosis of acute ischemic stroke seen at the ED of BJH between January 1, 2006, and December 31, 2007, who had a primary residence in St. Louis City or St. Louis County. St. Louis City is composed of 19 zip codes encompassing 62 square miles (160 km^2) in Missouri and has a population of approximately 347,000.[19] BJH is located in St. Louis City. St. Louis County is composed of 27 zip codes encompassing 508 square miles (1315 km^2) and has a population of approximately 1,000,000.[19] Subjects were excluded who were not home at the time of the stroke (eg, driving), experienced a seizure at the onset of stroke symptoms, had an address that could not be registered on the map of St. Louis City and County, or had an undetermined shortest distance from home to the hospital using the available software. Those with missing data on the outcomes of interest were excluded as well. Subjects with a low National Institute of Health Stroke Scale (NIHSS) score were not excluded because some of them had received tPA; however, those with an NIHSS score of 0 (no neurologic deficit) were excluded from the analysis of tPA use.

Exposure

The distance between each subject's home and BJH ED was the exposure of interest. Spatial data were compiled using Arc GIS Streetmap software (ESRI ArcGIS 9.2, Redlands, CA), which uses geographic information system (GIS) technology to create detailed street maps and perform point-to-point optimized routing.[20] The home address for each subject was geocoded to longitudinal and latitudinal coordinates and registered on a topographical street grid map of St. Louis City and County (Fig 1). The accuracy of geocoding was verified by onsite inspection of 10% of the addresses randomly sampled to represent at least half of the zip codes in the study area. A street network data set of all streets within the boundaries of St. Louis City and County was created. Using the street map network data set and the GIS network analysis Closest Facility application, the shortest route distance (ie, network distance)[21] between the patient's home and BJH ED via roads and highways was calculated. The fastest possible time that the subject could arrive at the BJH ED from his or her home was determined using modified TIGER map data that contained information on route speed limits. Subjects were then grouped by network distance into quintiles (first quintile, 0-2.634 miles, second quintile, >2.634-3.747 miles; third quintile, >3.747-4.594 miles; fourth quintile, >4.594-6.529 miles; fifth quintile, >6.529 miles) and further classified into 2 groups (group A, first quintile; group B, second through fifth quintiles) for the purpose of comparing those in close proximity to the hospital with those living further away.

Outcomes

The outcomes of interest were arrival time (ie, time between onset of stroke symptoms and ED arrival), timely arrival to the ED (ie, within 3 hours of stroke onset), and administration of tPA.

Covariates

The following variables were considered potential effect modifiers and confounders: age, race, sex, degree

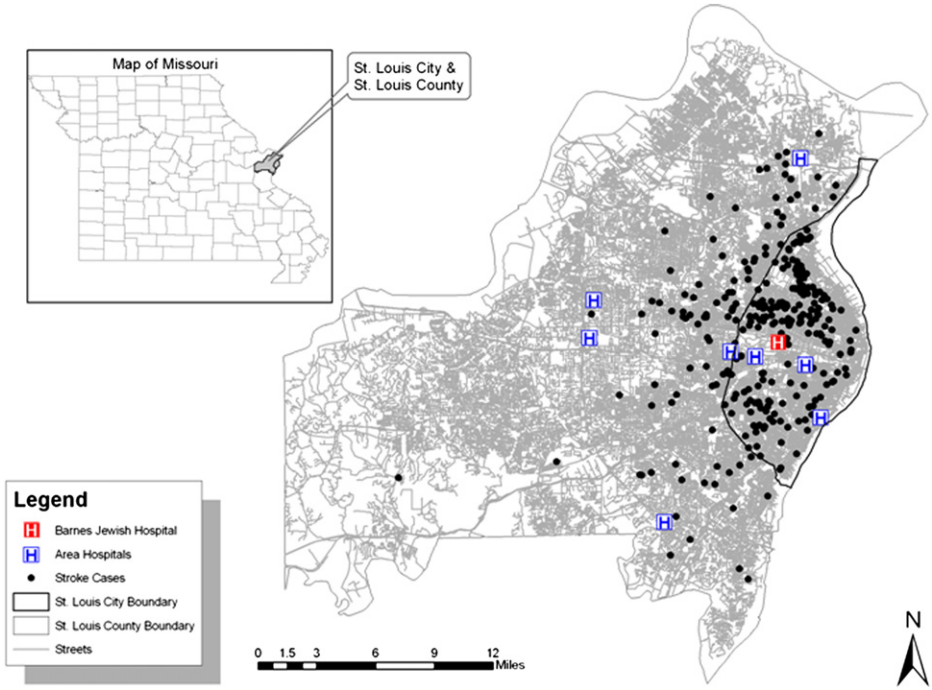

Figure 1. *Street grid map of St. Louis City and County showing the location of each subject in relation to BJH and other area hospitals.*

of neurologic deficit (as measured by NIHSS score), insurance status (insured vs noninsured), day of week (weekday vs weekend),[22] and arrival during rush hour (6-8 AM or 4-6 PM) versus non-rush hour. For the multivariate model, age and NIHSS score were dichotomized to aid interpretation. Age was dichotomized at 65 years, because this is generally the age of retirement and represents a significant life event. NIHSS score was dichotomized at a score of 10, with a score >10 considered a moderate to severe stroke. The NIHSS score was not tested as a continuous-level variable in the multivariate model because as an impairment scale, it is an ordinal-level variable.

Statistical Analysis

We evaluated for systematic differences between those included in the study versus those who were excluded for all baseline variables using χ^2 analysis, the independent *t* test (parametric variables), and the Mann-Whitney test (nonparametric variables). The correlation between network distance and arrival time was examined using Pearson's correlation coefficient. The rate of timely arrival (ie, within 3 hours of stroke onset) and rate of tPA administration were compared across quintiles of network distance, and the RRs for these outcomes were calculated for each quintile, using quintile 1 as the reference. Then the RR of timely arrival and tPA administration were calculated for group B subjects, using group A as the reference. This allowed the RR to represent the rate of the outcomes for those living further away with respect to those living in close proximity to the hospital.

We developed a multivariate model to correct for confounding and effect modification using log-binomial regression.[23] In this analysis, an additional 2 subjects were excluded because of missing data on NISSS score and/or race. Initially, we evaluated for differences between the 2 distance categories (group A vs group B) for each covariate using independent *t* test/Mann-Whitney and χ^2 analyses. If significant differences were seen and/or there were theoretical reasons why these factors could influence the relationship between exposure and outcome, then the covariates were tested for effect modification and confounding. Covariates were retained if their exclusion resulted in a change of ≥10% in the adjusted RR of the predictor variable (group B membership). Effect modification was tested using stratification analysis. In this model, the adjusted RR represented the rate of the outcome of interest for group B versus group A, with correction for the effect of covariates.

All statistical analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, IL), SAS 9.2 (SAS Institute, Cary, NC), and Epi Info (Centers for Disease Control and Prevention). This study was performed with the approval of the St. Louis University and Washington University Institutional Review Boards.

Results

From the original data set (n = 416), 86 cases were excluded: 55 cases because the index stroke occurred in a location outside the primary residence, 10 cases because of seizure at onset of stroke, 14 cases because their primary addresses could not be geocoded, 6 cases because

Table 1. *Baseline characteristics of subjects seen in the BJH ED for acute ischemic stroke, 2006-2007*

	Subjects Included (n = 330)	Subjects Excluded (n = 88)	*P* Value
Age, years, mean (SD), range	65.6 (15.6), 29-102	65.7 (15.9), 28-95	.98
Network distance, miles, mean (SD), range*	4.8 (2.9), 0-23.9	4.7 (2.8), 0.3-12.4	.72
Maximum speed, minutes, mean (SD), range†	9.6 (6.0), 0-47.8	9.4 (6.2), 0.7-36.2	.77
Average speed, minutes, mean (SD), range†	11.5 (7.4), 0-56	11.5 (8.7), 0.8-55.7	.98
Arrival time, minutes, median (IQR), range‡	126 (58-405), 0-5853	96 (52-371), 24-1943	.19
NIHSS score, median (IQR), range§	4.0 (1-8), 0-38	5.0 (1-10), 0-24	.81
Race, n (%)¶			.28
Caucasian	119 (36.1)	24 (27.6)	
African American	207 (62.7)	62 (71.3)	
Other	3 (0.9)	1 (1.1)	
Missing	1 (0.3)		
Female sex, n (%)	187 (56.7)	45 (51.7)	.31
Age ≥65 years, n (%)	167 (50.6)	41 (50.6)	.99
NIHSS score >10, n (%)	66 (20.1)	19 (23.5)	.50
Insurance status, n (%)‖			
Insured	294 (89.4)	71 (87.7)	.66
Medicare	160 (48.5)	40 (49.4)	.90
Medicaid	69 (20.9)	21 (25.9)	.34
Private insurance	195 (59.3)	44 (54.7)	.42
Uninsured	35 (10.6)	10 (12.3)	.66
Time of day, n (%)			.12
12:01-6:00 AM	30 (9.1)	4 (4.6)	
6:01-12:00 PM	82 (24.8)	15 (17.2)	
12:01-6:00 PM	137 (41.5)	45 (51.7)	
6:01-12:00 AM	81 (24.5)	23 (26.4)	
Weekend	92 (27.9)	23 (26.1)	.53
Rush hour, n (%)**			.08
Morning	12 (3.6)	3 (3.4)	
Evening	26 (7.9)	13 (14.9)	
Arrival time, n (%)			.87
1 hour	91 (27.6)	26 (29.9)	.28
2 hour	70 (21.2)	17 (19.5)	.36
3 hours	32 (9.7)	8 (9.2)	.41
4-6 hours	49 (14.8)	11 (12.6)	
>6 hours	88 (26.7)	21 (24.1)	
Missing	4 (4.6)		
TPA use, n (%)	45 (13.6)	12 (13.8)	.73

*Distance between subject's residence and hospital by roads/highways.
†Time to travel from residence to hospital if traveling by optimum route and going either the average speed or fastest speed allowed.
‡Time between stroke symptom onset and ED arrival. Because of a skewed distribution, the median and IQR are given.
§Missing NIHSS data (n = 1).
¶Other ethnicities/races include Hispanic and Asian (n = 3).
‖Subjects may have more than one type of insurance.
**Morning rush hour, 6-8 AM; evening rush hour, 4-6 PM.

the network distance between home and hospital could not be resolved, and 2 cases because of lack of data on tPA administration. This left 330 subjects available for analysis. There were no significant differences in baseline characteristics between the included subjects and excluded subjects (Table 1).

All subjects resided between latitude 38.47 and 38.79 and longitude −90.45 and −90.20. On 6 occasions, 2 subjects had the same address, suggesting that during the 2-year period, either 2 people at the same residence had been brought to the ED for stroke symptoms or the same individual had been brought twice. A total of 193 subjects (41.5%) arrived within 3 hours of stroke onset, 45 subjects (13.6%) received tPA.

The correlation between network distance and arrival time was not statistically significant ($P = .425$). Grouping subjects by network distance quintiles revealed no significant differences in the percentage who arrived at the ED within 3 hours (Table 2). Similarly, there was no significant difference in the rates of arrival within 2 hours and

Table 2. *Arrival time after stroke symptoms and administration of tPA by network distance from home to hospital in quintiles*

Network Distance*	Arrival Within 3 Hours of Stroke Onset, n (%), RR	Received tPA, n (%), RR†
Quintile 1 (0-2.634 miles)	42 (63.6), reference	14 (23.3), reference
Quintile 2 (>2.634-3.747 miles)	39 (59.1), 0.93 (0.71-1.22)	8 (14.5), 0.62 (0.28-1.37)
Quintile 3 (>3.747-4.594 miles)	33 (50.0), 0.79 (0.58-1.06)	5 (8.9), 0.38 (0.15-0.99)
Quintile 4 (>4.594-6.529 miles)	41 (62.1), 0.98 (0.75-1.27)	9 (16.4), 0.70 (0.33-1.49)
Quintile 5 (>6.529 miles)	38 (57.6), 0.90 (0.69-1.19)	6 (11.3), 0.49 (0.20-1.17)
P value, χ^2 test	.546	.238

*Each quintile has 66 subjects.
†Excluding subjects with NIHSS score of 0 (n 5 279; quintile 1, n 5 60; quintile 2, n 5 55; quintile 3, n 5 56; quintile 4, n 5 55; quintile 5, n 5 53).

within 1 hour (data not shown). Comparing the rate of arrival within 3 hours of stroke onset in group B and group A revealed no significant difference (57/100 vs 63/100, respectively), with an RR of 0.90 (95% CI, 0.73-1.11) for group B versus group A. Therefore, a multivariate model was not developed for the outcome of timely arrival.

For the outcome of tPA treatment, subjects with an NIHSS score of 0 were excluded, leaving 279 subjects available for analysis. The RR of tPA administration was lower in quintiles 2-5 compared with quintile 1, but this difference was statistically significant only when quintile 3 was compared with quintile 1 (Table 2). The percentage of subjects receiving tPA was lower in group B compared with group A (13/100 vs 23/100), with an RR of 0.55 (95% CI, 0.31-0.97) for group B compared with group A.

In developing the multivariate model for the outcome of tPA treatment, each covariate was compared between the 2 groups. There were no significant differences in baseline variables except for age and race. Group A had a higher mean age, a higher proportion of persons age ≥65 years, and a higher proportion of African Americans (Table 3); therefore, age and race were analyzed as potential confounders and effect modifiers in the model. NIHSS score and sex also were included in the full model, because the literature suggested that they might influence the likelihood of receiving tPA. Insurance status, as an indirect socioeconomic measure, was included as well. Arrival during rush hour and arrival during the weekend were not included, because there was no significant difference between the 2 groups for these variables and there was no theoretical reason to include them.

There was no significant effect modification. Age, race, sex, and insurance status were not statistically significant predictors of tPA administration, and their exclusion did not significantly affect the adjusted RR for the main predictor variable (group B membership), so these variables were eliminated from the model. NIHSS score >10 was a statistically significant predictor of tPA use ($P < .001$); eliminating this variable decreased the adjusted RR of group B membership by >10%.

For the final model, tPA treatment was the outcome, group B membership was the major predictor, and NIHSS score >10 was the sole confounder. The adjusted RR for tPA treatment for group B compared with group A was 0.59 (95% CI, 0.34-0.99). The adjusted RR of tPA treatment for subjects with an NIHSS score >10 compared with those with an NIHSS score of ≤10 was 3.78 (95% CI, 2.21-6.48).

Discussion

In this study, subjects living further from the hospital were >40% less likely to receive tPA for acute ischemic stroke than those living in close proximity to the hospital. Figure 2 shows the distribution of those who did and did not receive tPA. The group that received tPA was contained within a narrower geographical region around the hospital compared with those who did not receive tPA. However, many subjects who lived within close proximity to the hospital did not receive tPA, suggesting that other factors are important determinants as well. Many of the subjects who did not receive tPA resided closer to other community hospitals where treatment could have been administered. The reason why other hospitals were bypassed is unknown, but it might have been due to patient or physician preference, as well as to issues related to hospital diversion. Because of the time-sensitive nature of this treatment, rapid transport to the closest facility with experience in treating patients with tPA is generally desirable.

The finding that those living in close proximity to the hospital were more likely to receive tPA is not explained by earlier arrival times. There was no difference between those living close to the hospital and those living farther away in terms of arrival within 1, 2, or 3 hours after onset of stroke symptoms. However, in the first 3 quintiles, the percentage of subjects arriving within 3 hours decreased with increasing distance from the hospital. But in the fourth and fifth quintiles, these percentages increased. This finding may represent a different mode of transportation used by those arriving from farther away; namely, those in the fourth or fifth quintile might have traveled by ambulance, whereas those in the first, second, and third quintiles might have traveled by car. The data set does

Table 3. *Baseline differences by group membership*

	Group A (n = 66)	Group B (n = 264)	*P* Value
Age, years, mean (SD)	69.4 (15.7)	64.1 (15.4)	.03
Age ≥65 years, n (%)	43 (65.2)	124 (47.0)	.01
Race, n (%)			.02
Caucasian	16 (24.2)	103 (39.5)	
African American	50 (75.5)	157 (60.5)	

There were nonsignificant differences between groups for the following covariates: sex, NIHSS score, insurance status (insured vs noninsured), day of week (weekday vs weekend), and arrival during rush hour versus non–rush hour.

not contain data on the means of transportation to the hospital. Even subjects living the farthest away were still within 1 hour of the hospital if transported by the fastest route available (Table 1), suggesting that factors other than distance from the hospital were key determinants of timely arrival. We can speculate that those subjects who lived closer were more aware of available stroke treatments, but there are no available data to confirm or refute this possibility.

This study has several limitations. The subjects might not be representative of all stroke patients. In addition, good candidates for tPA therapy who lived further away might have been taken to outside hospitals, which would result in a lower rate of tPA administration in subjects from those areas. In addition, the accuracy of information on time of onset of symptoms cannot be independently verified. The data set did not include data on the presence of resolving symptoms, which might have accounted for some of the subjects not receiving tPA. There is no reason to believe that the proportion of subjects with resolving symptoms was higher in group B than in group A, however.

One assumption in our data analysis was that subjects would take (or would be taken) on the shortest route at the fastest speed allowable. Most ambulances used in St Louis City and County are equipped with a GPS system, which allows optimization of routes. It is possible that an ambulance may have traveled a different route because of local traffic conditions or road construction. Although the means of arrival is not known, it is very unlikely that any of the subjects arrived by means other than ground transportation.

Many factors play a role in timely arrival at the ED after stroke onset, including recognition of stroke symptoms, time to activation of the emergency medical system and arrival of the ambulance, and time taken to transport the subject to the ED. The data suggest that even those living relatively farther away from the hospital can arrive within 1 hour of onset of stroke symptoms if transportation is initiated immediately. To the best of our knowledge, this is the first study suggesting that those living within close proximity to a hospital are more likely to receive tPA. These findings need to be replicated in other

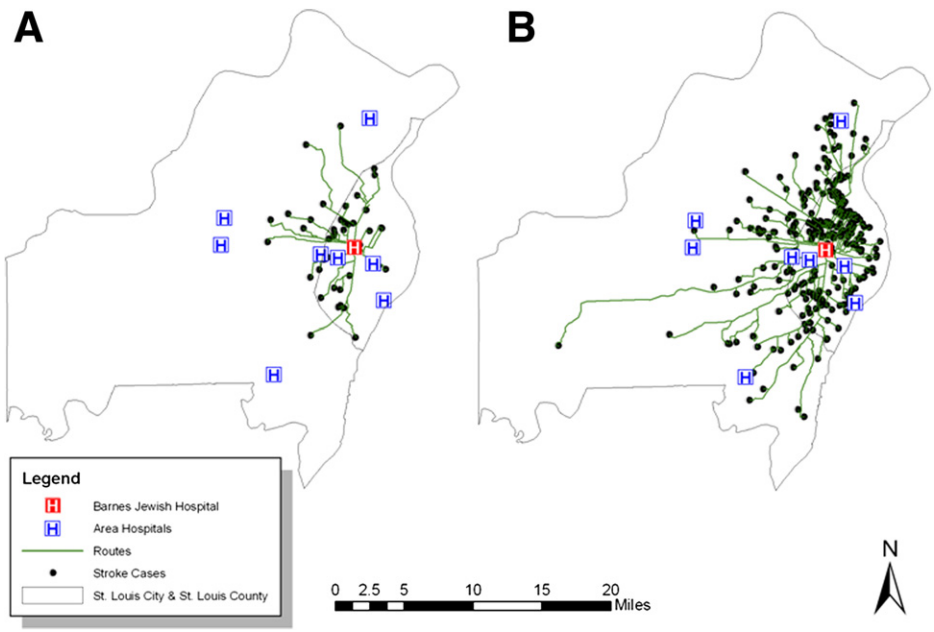

Figure 2. *Map of St Louis City and County showing the routes taken by those who did (A) and did not (B) receive tPA treatment for acute ischemic stroke.*

settings, especially nonurban settings, in which the distances between home and hospital might be greater.

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