ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Association of Geographical Factors With Administration of Tissue Plasminogen Activator for Acute Ischemic Stroke

Susumu Kunisawa, MD; Toshitaka Morishima, MD, PhD; Naoto Ukawa, DDS; Hiroshi Ikai, MD, PhD; Tetsuya Otsubo, PhD; Koichi B. Ishikawa, PhD; Chiaki Yokota, MD, PhD; Kazuo Minematsu, MD, PhD; Kiyohide Fushimi, MD, PhD; Yuichi Imanaka, MD, PhD

***Background*—**Intravenous tissue plasminogen activator (tPA) is an effective treatment for acute ischemic stroke if administered within a few hours of stroke onset. Because of this time restriction, tPA administration remains infrequent. Ambulance use is an effective strategy for increasing tPA administration but may be influenced by geographical factors. The objectives of this study are to investigate the relationship between tPA administration and ambulance use and to examine how patient travel distance and population density affect tPA utilization.

***Methods and Results*—**We analyzed administrative claims data from 114 194 acute ischemic stroke cases admitted to 603 hospitals between July 2010 and March 2012. Mixed-effects logistic regression models of patients nested within hospitals with a random intercept were generated to analyze possible predictive factors (including patient characteristics, ambulance use, and driving time from home to hospital) of tPA administration for different population density categories to investigate differences in these factors in various regional backgrounds. Approximately 5.1% (5797/114 194) of patients received tPA. The composition of baseline characteristics varied among the population density categories, but adjustment for covariates resulted in all factors having similar associations with tPA administration in every category. The administration of tPA was associated with patient age and severity of stroke symptoms, but driving time showed no association. Ambulance use was significantly associated with tPA administration even after adjustment for covariates.

***Conclusion*—**The association between ambulance use and tPA administration suggests the importance of calling an ambulance for suspected stroke. Promoting ambulance use for acute ischemic stroke patients may increase tPA use. **(*J Am Heart Assoc.* 2013;2:e000336 doi: 10.1161/JAHA.113.000336)**

Key Words: emergency medical services • health services research • ischemic stroke • tissue-type plasminogen activator

The administration of intravenous tissue plasminogen activator (tPA) has been shown to improve prognoses after acute ischemic stroke.[1,2] This treatment was approved in October 2005 in Japan but is still infrequently used because appropriate tPA administration is time dependent and limited to patients within a few hours of acute ischemic stroke onset.[3–7] Additionally, regional differences for the use of tPA have been reported.[8]

Because the use of this treatment is dependent on the time elapsed from stroke onset, emergency medical services use and geographical factors can be expected to influence tPA administration. Several studies have reported the benefits of ambulance use for stroke care,[9–11] and educational campaigns to promote the calling of an ambulance for suspected stroke patients have been carried out in Australia[12] and Japan.[13]

Geographical factors in health care frequently involve the distance between patient residences and hospitals. Some studies have reported an association between patient distance and delayed hospital arrival,[14,15] whereas another study found no association.[16] However, these studies have generally been conducted using relatively small sample sizes and were performed at the hospital or regional level. Another geographical factor that should be considered is the degree of urbanization of a region, as hospital-seeking behavior may differ depending on the availability and proximity of hospitals.

From the Department of Healthcare Economics and Quality Management, Graduate School of Medicine, Kyoto University, Kyoto, Japan (S.K., T.M., N.U., H.I., T.O., Y.I.); Economics Section, Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan (K.B.I.); Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan (C.Y.); National Cerebral and Cardiovascular Center, Suita, Japan (K.M.); Department of Health Policy and Informatics, Tokyo Medical and Dental University, Tokyo, Japan (K.F.).

Correspondence to: Yuichi Imanaka, MD, PhD, Department of Healthcare Economics and Quality Management, Graduate School of Medicine, Kyoto University; Yoshida Konoe-cho, Sakyo-ku, Kyoto City, Kyoto, Japan 606-8501. E-mail: imanaka-y@umin.net

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From this perspective, a large interregional database is necessary for an in-depth analysis of factors associated with tPA use.

Recent advances in computing capabilities have increased the potential for various analytical methods. In Japan, the Diagnosis Procedure Combination Per-Diem Payment System (DPC/PDPS), which was introduced to acute care hospitals in 2003, requires that hospitals generate standardized DPC data for each patient per hospitalization. DPC data are administrative claims data that also include a summary of clinical information. These data are collected by the national government, which conducts an annual review at the individual hospital level; the reports of these results, including that of data quality, are available to the public.[17] This periodic review for the data quality assurance system has continued to be conducted, thereby ensuring a high standard of quality for the data. Since July 2010, DPC/PDPS requires the collection of additional information, such as each patient's residence postal code, neurological deficits, and date of stroke onset. The uniform formatting of DPC/PDPS data forms allows the collection, handling, and analysis of large quantities of administrative data from numerous hospitals located nationwide. This database also allows analyses that take into account critical differences in patient case mix.

The objectives of this study were to investigate the relationship between tPA administration and ambulance use and to investigate how distance and population density differences affect the use of this treatment. Analyses that not only use a large database but also account for case mix and regional differences can offer more useful evidence than previously available.

Methods

Data Source

This study used data extracted from the DPC database for patients hospitalized between July 2010 and March 2012. The data were collected by the DPC Study Group, which is funded by the Japanese Ministry of Health, Labour and Welfare. The hospitals participating in the DPC Study included "approximately 3 million inpatients each year, or ≈40% of all acute care hospital admissions in Japan."[18] Driving times to the admitting hospitals were calculated using geographical information system software for the shortest path via open road from each patient's home postal code location. These times reflect driving at speeds set for specific road categories based on road width. Although traffic conditions were not taken into consideration in calculating drive times, regular waiting times at intersections en route were included in the estimates. We calculated driving times up to 90 minutes, and a preliminary analysis showed that 99.2% of national population resided within 90 minutes from the nearest acute hospital.

Patient Selection

We selected patients of at least 18 years of age who were admitted for acute ischemic stroke, and had complete information available for the variables of interest. Acute ischemic stroke was identified by the *International Classification of Diseases 10th Edition* diagnosis code "I63$" with stroke onset occurring on the date of admission. The use of an ambulance was also registered in the same database. In Japan, both medical staff and individuals can call for an ambulance without incurring additional charges for patients. Ambulances arrive quickly, with average arrival times reported at ≈7 minutes.[19] "Ambulance use" in DPC data is defined as the direct transportation from the scene of the event to the hospital by ambulance. We also selected patients who resided within 90 minutes driving time from the hospital. We further limited our analysis to hospitals that had discharged ≥1 patients who had been administered tPA during the study period, because tPA is only available at hospitals that meet certain criteria.[3] Consequently, the analysis included a total of 114 194 cases from 603 hospitals.

Consciousness and Physical Impairment Levels

Consciousness levels were determined using the Japan Coma Scale (JCS), which uses the following grades: grade 0 (alert), grade I (awake without any stimuli), grade II (arousable), and grade III (unarousable).[20,21]

The level of physical impairment was determined using the modified Rankin Scale (mRS) scoring system. The mRS is principally used to evaluate activities of daily living (ADLs) for assessing disability and dependence of a patient after stroke,[22] but DPC data include patient mRS scores at admission as a substitute for assessing physical impairment for acute ischemic stroke patients. The mRS was selected because its assessment is relatively easy and the uniformly formatted data of the DPC database require a common scale of input for any type of stroke. We reduced the mRS from the original 6 classes to the following 3: 0 to 2 (mild), 3 to 4 (moderate), and 5 (severe).

Hospital Area

Because population density is one of the most widely used and accepted indicators of the level of urbanization,[23] we categorized hospitals according to the population density of the secondary medical area of each hospital to identify relatively rural and urban areas. Secondary medical areas in

Japan are government-designated subprefectural regional units that are autonomously capable of supplying inpatient medical services to meet the demand within that region. These services include the majority of general medical and surgical services, excluding some specialized treatments.[24] We calculated population density using data provided by the government in 2010[25,26] and generated 3 classes according to these data: <300 persons/km^2, 300 to 1000 persons/km^2, and >1000 persons/km^2.

Statistical Analysis

We used mixed-effects logistic regression models with a random intercept for patients nested within hospitals to identify independent factors associated with tPA administration. A multilevel approach was taken to account for possible clustering of tPA administration in hospitals. The analysis included a total of 4 regression models: 1 for each of the 3 population density categories and 1 with all cases in this study. A 2-tailed test was performed with P values <0.05 considered significant using SPSS software version 20.0.0.2 (IBM). Discrimination of the regression models was evaluated with C-statistics.

Ethical Standard

This study was approved by the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine.

Results

Table 1 shows the baseline characteristics and tPA use of the study sample by population density of the secondary medical area served by each hospital. In general, each category had similar baseline characteristics, but there were more elderly patients and patients residing further from hospitals in lower population density areas (P<0.05 using χ^2 test). For the 3 population density categories of <300 persons/km^2, 300 to 1000 persons/km^2, and >1000 persons/km^2, the percentages of patients aged 75 years or older were 61%, 55%, and 51%, respectively; and the percentages of patients who had a driving time of ≥30 minutes were 36%, 29%, and 17%,

Table 1. Administration of Tissue Plasminogen Activator (tPA) to Acute Ischemic Stroke Patients by Patient Variables and Population Density of Hospital Secondary Medical Areas

		Population Density of Medical Area, persons/km^2			
tPA Use Rate, % (tPA No. of Uses/Cases)		<300	300 to 1000	>1000	All
Gender	Male	4.8% (773/16 064)	5.2% (1101/21 042)	5.2% (1514/29 225)	5.1% (3388/66 331)
	Female	4.5% (565/12 614)	5.3% (811/15 227)	5.2% (1033/20 022)	5.0% (2409/47 863)
Age, y	18 to 64	4.7% (228/4843)	5.7% (421/7362)	4.9% (516/10 491)	5.1% (1165/22 696)
	65 to 74	5.6% (355/6380)	5.8% (514/8918)	5.9% (789/13 373)	5.8% (1658/28 671)
	75 to 84	5.1% (543/10 612)	5.3% (660/12 418)	5.3% (852/16 163)	5.2% (2055/39 193)
	≥85	3.1% (212/6843)	4.2% (317/7571)	4.2% (390/9220)	3.9% (919/23 634)
Consciousness grade at admission	Alert	1.8% (230/12 798)	2.3% (402/17 655)	1.9% (465/24 782)	2.0% (1097/55 235)
	Awake	5.8% (654/11 253)	6.6% (849/12 896)	7.2% (1217/16 865)	6.6% (2720/41 014)
	Arousable	10.9% (322/2944)	13.1% (488/3735)	12.6% (632/5012)	12.3% (1442/11 691)
	Unarousable	7.8% (132/1683)	8.7% (173/1983)	9.0% (233/2588)	8.6% (538/6254)
Physical impairment at admission	Mild	1.1% (82/7654)	1.1% (115/10 409)	1.3% (204/15 359)	1.2% (401/33 422)
	Moderate	3.9% (493/12 714)	4.6% (744/16 133)	4.8% (1065/21 988)	4.5% (2302/50 835)
	Severe	9.2% (763/8310)	10.8% (1053/9727)	10.7% (1278/11 900)	10.3% (3094/29 937)
Driving time from patient residence to the hospital	<15 min	4.8% (421/8776)	5.1% (620/12 217)	5.0% (1114/22 404)	5.0% (2155/43 397)
	15 to 29 min	4.5% (430/9457)	5.2% (689/13 210)	5.4% (977/18 202)	5.1% (2096/40 869)
	30 to 59 min	4.5% (359/7926)	5.5% (489/8877)	5.2% (379/7323)	5.1% (1227/24 126)
	60 to 90 min	5.1% (128/2519)	5.8% (114/1965)	5.8% (77/1318)	5.5% (319/5802)
Arrival by ambulance	No	1.4% (191/13 885)	1.5% (254/16 836)	1.1% (226/20 240)	1.3% (671/50 961)
	Yes	7.8% (1147/14 793)	8.5% (1658/19 433)	8.0% (2321/29 007)	8.1% (5126/63 233)
Total		4.7% (1338/28 678)	5.3% (1912/36 269)	5.2% (2547/49 247)	5.1% (5797/114 194)

Table 2. Results of Multivariable Logistic Regression Analyses With Tissue Plasminogen Activator Administration for Acute Ischemic Stroke Patients as the Dependent Variable, Classified by Population Density of Hospital Secondary Medical Areas

	Population Density of Medical Area, persons/km^2			
	<300	300 to 1000	>1000	All
Gender (referent: male)	0.96 (0.85 to 1.08)	0.98 (0.88 to 1.09)	0.96 (0.88 to 1.06)	0.97 (0.91 to 1.03)
Age (referent: 18 to 64 y)				
65 to 74 y	0.96 (0.80 to 1.16)	0.82 (0.71 to 0.95)*	0.93 (0.82 to 1.05)	0.90 (0.83 to 0.97)*
75 to 84 y	0.65 (0.55 to 0.78)**	0.56 (0.48 to 0.64)**	0.63 (0.56 to 0.72)**	0.61 (0.56 to 0.66)**
≥85 y	0.27 (0.22 to 0.34)**	0.31 (0.27 to 0.37)**	0.36 (0.31 to 0.42)**	0.32 (0.29 to 0.35)**
Consciousness grade at admission (referent: alert)				
Awake	2.14 (1.81 to 2.54)**	1.88 (1.64 to 2.16)**	2.71 (2.41 to 3.06)**	2.29 (2.11 to 2.47)**
Arousable	3.03 (2.47 to 3.72)**	2.74 (2.32 to 3.24)**	3.63 (3.14 to 4.20)**	3.19 (2.89 to 3.51)**
Unarousable	1.74 (1.35 to 2.25)**	1.50 (1.21 to 1.86)**	2.21 (1.83 to 2.66)**	1.84 (1.63 to 2.08)**
Physical impairment at admission (referent: mild)				
Moderate	2.86 (2.24 to 3.65)**	3.40 (2.76 to 4.17)**	2.53 (2.16 to 2.97)**	2.85 (2.55 to 3.19)**
Severe	5.93 (4.59 to 7.66)**	6.50 (5.22 to 8.09)**	4.36 (3.68 to 5.17)**	5.29 (4.69 to 5.95)**
Driving time from patient residence to the hospital (referent: <15 min)				
15 to 29 min	0.93 (0.80 to 1.08)	0.97 (0.86 to 1.09)	0.97 (0.88 to 1.07)	0.96 (0.90 to 1.03)
30 to 59 min	0.86 (0.74 to 1.01)	0.95 (0.83 to 1.09)	0.92 (0.81 to 1.05)	0.92 (0.85 to 0.99)*
60 to 90 min	0.92 (0.74 to 1.15)	0.98 (0.78 to 1.23)	1.06 (0.82 to 1.37)	0.98 (0.86 to 1.12)
Arrival by ambulance	3.63 (3.07 to 4.28)**	3.91 (3.39 to 4.51)**	4.55 (3.94 to 5.25)**	4.06 (3.72 to 4.42)**
C-statistic of the model	0.834	0.834	0.826	0.831

**P*<0.05, ***P*<0.01.

respectively. Overall, 55.4% (63 233/114 194) of the patients used an ambulance. A total of 5.1% (5797/114 194) of the patients received tPA during hospitalization, and the tPA use rates by baseline characteristics were similar among the 3 population density categories.

Table 2 shows the results of the mixed-effects logistic regression analyses. The odds ratios calculated were similar in all models. Elderly patients received tPA less frequently than younger patients, and stroke severity was found to be positively associated with tPA administration up to a certain level. On the other hand, driving times from home to hospital were not associated with tPA use. After adjusting for all other factors, ambulance use showed significant association with tPA administration. The discrimination of the regression models was high, with C-statistics for each model having values >0.82.

Discussion

The administration rate of tPA for acute ischemic stroke patients in this study was 5.1% (5797/114 194). Patient baseline characteristics such as age and driving time differed among the population density categories and were consistent with expectations for rural and urban areas. The associations of each factor on tPA use were similar across the categories after adjustment in each regression model. Notably, ambulance use was significantly associated with tPA use, whereas driving time from home to hospital was not.

A novel finding of our study is that distance from home to hospital was not associated with tPA use. These results were strengthened by the similar findings regardless of the level of urbanization, given by population density. However, this may be characteristic of countries with relatively few inhabitable regions, such as Japan, where a greater proportion of the population may live closer to hospitals compared with more expansive countries. As a result, the number of patients residing far from hospitals in this study was so small that they would likely have little effect in the regression models. Most of the independent variables had similar coefficients among the 3 population density categories, suggesting that the results were consistent in regions regardless of the level of urbanization. However, it should be kept in mind that the geographical situation may be different in other countries; in more expansive countries, driving times of >90 minutes may be more common and such cases should be included in analyses. Despite this, we believe that the findings demonstrated in this study may not be unique to Japan (eg, 79% of adults in the United States have been shown to reside within 60 minutes of a hospital that provides acute cardiac therapy)[27] and that our results may also have applications in other countries.

Another novel finding is that ambulance use showed significant association with tPA administration even after adjustment for variations in patient characteristics. Ambulance use may affect transportation time and reduce delays in work flow during the admission process at the hospital, thereby increasing the chances of a patient being eligible for tPA administration.[10,11] This association was confirmed in this study using administrative data and available clinical information from the DPC database, which allowed a large-scale analysis. As our results show, it is important to adjust for factors such as patient age and stroke severity when analyzing tPA use. Furthermore, because this analysis had taken geographical differences into account, our findings that the adjusted effects of each factor on tPA use were similar in every population density category may have considerable external validity.

These results emphasize that promptly calling for an ambulance without hesitation can be important for suspected stroke patients,[5,12,13] as our study showed that only 55% of stroke patients used an ambulance despite the fact that their use is free of charge in Japan. Educational campaigns to help people recognize stroke symptoms in themselves and others are favorable as these have shown to increase the number of ambulance calls for acute ischemic stroke.[12] Because the decision to call for an ambulance may be influenced by factors other than those included in this study, further research should be conducted to investigate these possible relationships. In addition to promoting ambulance use, it is important to review and improve ambulance availability in each community.[28]

Another notable finding of this analysis is that the odds ratios for patient background characteristics were consistent both with guidelines and our clinical experiences. Here, older patients and those with the lowest stroke severity were less likely to receive tPA. This was congruous with guidelines that express caution for tPA administration in elderly patients.[6,7] On the other hand, an ambulance call is more likely to be delayed for an elderly individual,[29,30] which may also affect their eligibility for tPA administration. Similarly, guidelines do not recommend tPA use for patients with minor neurological symptoms,[3,5] and these patients are also associated with delayed calls for an ambulance.[5,15,29–32] Although we cannot determine any causal relationships from our analysis, our findings are consistent with those from previous reports.

One limitation of this study is that we only included hospitals that discharged at least 1 patient who was administered tPA during hospitalization. Consequently, this study does not address why some hospitals never used tPA for acute stroke patients, nor can it shed light on the circumstances of hospitals or regions that did not administer tPA. Other studies are needed to investigate these issues in the future.

Another limitation is the use of mRS as a measure of physical impairment at admission. Although this is not an orthodox application, these assessments were actually carried out to assess stroke symptoms, and DPC data included no other scale for evaluating physical impairment. Consequently, we found this measurement to be significantly associated with tPA use, and it may therefore have applications as a proxy indicator of physical impairment severity in acute stroke patients for predicting tPA use.

Next, although the database provides information on the date of stroke onset, it lacks information on the time of onset, which precluded us from investigating the detailed time lags from onset to hospital arrival. However, we limited our analysis to stroke patients whose onset was the day of admission, thereby minimizing these time lags. Although further analyses using time data are desirable, we believe our findings still have validity in showing the association of factors with tPA use.

Conclusions

Data from a large administrative claims database showed that tPA was administered in 5.1% of acute ischemic stroke cases. Analysis of factors affecting tPA administration using case mix adjustment methods showed that the distance from home to hospital was not associated with the use of this treatment, whereas ambulance use was highly associated with tPA administration, regardless of population density. Our study further supports and emphasizes that ambulance calls may represent one of the most important factors for suspected stroke patients.

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