

Impact of Day of the Week and Time of Arrival on Ischemic Stroke Management

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Objective: The purpose of this study was to evaluate the association between measures of patient arrival day (weekday or weekend day), day part (nighttime vs. daytime) and hour (regular hours vs. off hours) at the stroke unit of the Emergency Department of the Puerto Rico Medical Center and the following time-to-treatment measures: door-to-CT-scan, door-to-needle, and stroke-onset-to-treatment.

Methods: In this retrospective study, the data of 54 patients was obtained from the stroke unit of the Puerto Rico Medical Center through the Get With The Guidelines-Stroke Registry. Inclusion criteria were as follows: having an ischemic stroke within the period covering from August 2008 through February 2010 and being at least 18 years old. Associations between patient arrival time and timeliness of interventions were assessed using t-tests/Mann-Whitney tests and chi-square tests/Fisher's exact tests, as appropriate.

Results: The majority of the patients (74%) were men. The mean and standard deviation of age was 67 ± 14 years. The median of times for door-to-CT-scan and onset to treatment were 15 minutes (interquartile range = 15) and 2.7 hours (interquartile range = 0.6), respectively. The mean and standard deviation for door-to-needle time was 77 ± 18 minutes. No differences were found for any of the variables in terms of arrival date, day part or hour ($p > 0.05$). The median time for door-to-CT-scan was shorter for patients receiving intravenous tissue plasminogen activator treatment than it was for those not receiving such treatment (12 minutes vs. 20 minutes; $p = 0.02$).

Conclusion: The timeliness of the stroke management interventions did not differ significantly in terms of arrival day, day part, or hour. [*P R Health Sci J* 2015;34:164-169]

Key words: Acute Ischemic Stroke Management, Door to Needle, Ischemic Brain Disease, Intravenous Thrombolytic Treatment, Weekend Effect

Stroke is the 4th leading cause of death in United States (US), and its prevalence is expected to increase 20.5% by 2030 (1). In Puerto Rico, stroke is the 5th leading cause of death (2). The estimated prevalence of this disease for the Hispanic/Latino population in the US is 2.6% (3), while the overall estimated prevalence is 3.0% (1). Hispanics and whites have been reported to receive similar qualities of ischemic stroke (IS) care within US hospitals (4). There is limited information about stroke epidemiology and treatment in Hispanic populations, including that of Puerto Rico.

Early recognition and acute stroke treatment will produce better patient outcomes by reducing patient mortality and morbidity. A reduction in mortality and morbidity could be achieved by better controlling risk factors, by facilitating the early recognition of warning signs and symptoms, by minimizing medical complications, and by providing timely, adequate treatment (5,6). Throughout the literature, the simultaneous needs to reduce the time from symptom(s) onset to arrival and door-to-needle time (DNT) are emphasized. In this article, "door" refers to the moment of arrival at the emergency

department, and "needle" refers to the moment at which thrombolytic treatment is administered (7–11). The therapy's effectiveness decreases as the time from symptom(s) onset increases, and the timely administration of therapy will improve outcomes (7–12). Educating patients and hospital staff on the importance of early detection and symptom recognition could facilitate the initiation of intravenous thrombolytic treatment within a 4.5-hour window of treatment after symptom onset (13). Intravenous tissue plasminogen activator (IVtPA) is an

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approved intravenous thrombolytic treatment that improves stroke outcomes. Starting treatment within the established 0- to 4.5-hour window of treatment after symptom onset reduces patient disability and mortality (8). The arrival day and time, the admission day (that is, the particular day of the week), and the length of stay are other time measurements taken into consideration in terms of finding ways to improve treatment timeliness (5).

Several publications have suggested that the variable quality of care during off hours, known as the “weekend effect,” can result in higher mortality risk and delays in the initiation of recommended clinical interventions for stroke patients (14–16). No information regarding whether or not the so-called weekend effect is responsible for compromising or otherwise affecting the management of ischemic stroke patients visiting the Puerto Rico Medical Center stroke unit currently exists.

The purpose of this study was to evaluate the association between the measures of the arrival times, day part and hour (regular vs off hours) of potential ischemic stroke patients referred by the Emergency Department (ED) to the stroke unit (SU) of the Puerto Rico Medical Center and the measures of the timeliness of stroke management interventions (door-to-CT-scan, door-to-needle, and stroke onset-to-treatment) at the SU.

Methods

Data source

In this retrospective study, we used a secondary database to assess the impact that patient arrival day of the week time, day part and hour at the ED may have on stroke management interventions among potential ischemic stroke patients referred to the SU. The stroke unit, an emerging comprehensive stroke center, is part of the Puerto Rico Medical Center, which is itself an island-wide, academic medical center and tertiary care facility serving mainly the government-insured and noninsured patients of Puerto Rico and the Caribbean. The secondary database was created from data obtained at the stroke unit of the Puerto Rico Medical Center, which voluntarily participates in the “Get With The Guidelines-Stroke” (GWTG-S) registry, a stroke management and quality-improvement program sponsored by the American Heart Association/American Stroke Association (5). GWTG-S is an in-hospital program for improving stroke care by ensuring consistent adherence to the latest scientific treatment guidelines. As part of the process, the information of all patients evaluated in the SU is entered by the unit’s coordinator into the GWTG-S database. This information includes the patient’s medical history and demographics, treatment timeliness, and stroke management strategies. The GWTG-S Patient Management Tool is an online primary database and interactive assessment and reporting system. The AHA/ASA authorized the use of GWTG data for the purpose of this study.

In order to assess the pertinent time measures, the Patient Management Tool was used to gather the following data for our study: symptom onset date and time, arrival date and time,

admission date, brain imaging (25-minute window), treatment with IVtPA (<4.5-hour window), and time-to-IVtPA initiation (60-minute window). In addition, information on stroke severity using the National Institutes of Health Stroke Scale (NIHSS) and socio-demographic data were also included in our study. The information of all patients evaluated in the stroke unit was entered into the GWTG-S database.

Inclusion criteria for this study were as follows: having an ischemic stroke within the period covering from August 2008 through February 2010 and being at least 18 years old. All the patients evaluated in the SU (n = 74) during the study period were initially included in the study. Individuals with a diagnosis of hemorrhagic stroke and/or a transient ischemic attack (n = 20) were excluded from the study. Figure 1 show the participant recruitment process and group categorization. The final group for this analysis comprised 54 patients. The Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus, approved this study.

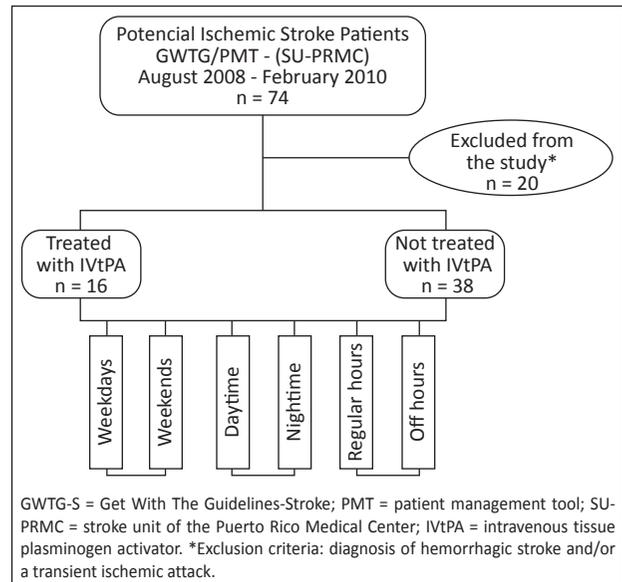


Figure 1. Flowchart of study participants and exposure categories; this chart shows the number of eligible participants and how their data were categorized, according to the type of exposure (that is, that they were treated or not treated with intravenous tissue plasminogen activator and, when treated, the day, day part, and hour of its occurrence).

Definitions

We evaluated the associations between 3 different measures of patient arrival time (exposures) at the ED and measures of timeliness of stroke management interventions in the SU (outcomes). The measures of arrival time assessed in this study were the following: day of arrival, day part, and hour. Days of arrival at the ED were categorized as weekdays (Monday through Friday) or weekend days (Saturday or Sunday; holidays were included). The day part at which a given individual arrived at the ED was categorized as daytime (from 08:00 to 16:00) or as nighttime (from 16:01 to 7:59). Hours of arrival at the ED were

categorized as falling within regular hours or within off hours. Regular hours were defined as Monday through Friday from 08:00 to 16:00. Off hours were defined as Monday through Friday from 16:01 to 07:59 and Friday at 16:01 through Monday at 07:59, or any time during a holiday. The work schedule of the SU personnel was used to define the time groups. As shown in Figure 1, treatment with IVtPA was considered as an exposure to treatment for the evaluation of door-to-CT-scan time.

The measures of the timeliness of stroke management interventions defined for this study were the following: door-to-CT-scan, door-to-needle, and stroke onset-to-treatment time. Door-to-CT-scan time was defined as the period of time (in minutes) from when a patient arrives at the ED until a CT scan is performed on this patient. Door-to-needle time was delimited to the time (in minutes) at which a patient arrives at the ED until the administration of IVtPA to that patient. Lastly, stroke onset-to-treatment time was defined as the amount of time (in hours) that passes from onset of a patient’s stroke symptoms to the initiation of IVtPA treatment in that patient.

Data analysis

Descriptive statistics were used to characterize the variables for each arrival measure. The normality of distribution of continuous variables was evaluated with the Shapiro–Wilk test. A t-test was used to compare continuous outcomes between exposure groups unless data were not normally distributed, in which case we used the Mann–Whitney test. Differences in gender distribution between exposure groups were assessed using a chi-square test or Fisher’s exact test, as appropriate.

The sample size differed for some analyses because of missing data related to the exposure and outcome variables. The NIHSS was not informed about 3 participants, while information on door-to-CT-scan time was missing for 20 of 54 patients included in the study; most of these 20 patients arrived on a weekday (85%), during the daytime (80%), and during regular hours

(65%). Data regarding door-to-needle and stroke onset-to-treatment time were measured for only those 16 patients who were treated with IVtPA.

A p-value of less than 0.05 was considered statistically significant for all tests. All statistical analysis was performed using STATA software, v. 11.2 (Stata Corp., L.P., College Station, TX).

Results

Table 1 shows the demographic data of the study group and the severity of the ischemic stroke, by day, day part and hour of arrival. Men comprised the majority (74%) of the SU sample group. The mean age, taking into account all individuals studied was 67 (± 14) years. Neither gender nor age differed significantly between arrival categories (p>0.05). Most individuals in this study arrived at the ED during off hours (61%), daytime (57%), or weekdays (72%). The mean values of stroke severity among all ischemic stroke patients assessed in this study were 8.4 (± 5.6); stroke severity was not significantly different between exposure categories (p>0.05 for all exposures). Only 16 (30%) out of 54 individuals in our study were treated with IVtPA. Most of the patients receiving the IVtPA treatment visited the ED on weekdays (81%), at night (56%), or during off hours (63%).

We found that the median onset-to-arrival time was 9.8 hours (95% CI: 4.9–60.1) for the non-treated cases, whereas the treated cases had a median onset-to-arrival time of 1.8 hours (95% CI: 1.1–2.4). The overall mean of time from onset to treatment was 3.0 (± 1.0) hours. The overall door-to-needle time mean was 77 (± 18) minutes. Table 2 shows (by arrival category) the timeliness of IVtPA treatment for ischemic stroke patients in our study. No statistically significant differences were found for door-to-needle or onset-to-treatment variables by arrival date, day part or hour (p>0.05).

For the 54 ischemic stroke patients, both those receiving IVtPA and those not receiving IVtPA, the overall median of the door-to-CT-scan was 15 minutes (interquartile range [IQR] = 15). The median of time from door-to-CT-scan was shorter for patients treated with IVtPA (median = 12, IQR = 5) than it was for those not treated with IVtPA (median = 20, IQR = 17; p = 0.02; Figure 2). However, no differences were found between arrival exposure

Table 1. Description of Ischemic stroke patients in terms of arrival day, day part and hour (n = 54)

	Arrival Day			Arrival day part			Arrival Hour		
	Weekdays	Weekends	p-value*	Daytime	Nighttime	p-value*	Regular hours	Off hours	p-value*
	n = 39	n = 15		n = 31	n = 23		n = 21	n = 33	
	n (%)			n (%)			n (%)		
Sex									
Male	29 (74)	11 (73)	>0.99†	23 (74)	17 (74)	0.98	16 (76)	24 (73)	0.78
Female	10 (26)	4 (27)		8 (26)	6 (26)		5 (24)	9 (27)	
	Mean ± SD			Mean ± SD			Mean ± SD		
	Median (IQR)			Median (IQR)			Median (IQR)		
Age, years	67 ± 13	70 ± 14	0.43	65 ± 14	71 ± 13	0.11	64 ± 15	69 ± 13	0.18
	68 (20)	66 (25)		62 (19)	70 (25)		61 (21)	70 (16)	
NIHSS[^]	7.9 ± 5.2	9.6 ± 6.5	0.45‡	7.8 ± 5.0	9.2 ± 6.3	0.57‡	7.9 ± 4.9	8.7 ± 6.0	0.62
	7.0 (9.0)	9.0 (8.0)		6.0 (7.0)	10 (11)		7.0 (8.0)	8.5 (9.0)	
N missing	2	1		2	1		0	3	

*A chi-square test or t-test, as appropriate, was used to compare groups, unless otherwise specified; †Fisher’s exact test was performed; ‡A Mann–Whitney test was performed; ^The National Institutes of Health Stroke Scale (NIHSS) was used to determine stroke severity; not reported for 3 patients. Stroke severity values between 5 and 15 indicate a moderate stroke.

Table 2. Timeliness of ischemic stroke patient treatment, by arrival day, day part and hour (n = 16).*

	Arrival Day		p-value†	Arrival day part		p-value†	Arrival Hour		p-value†
	Weekday n = 13	Weekend n = 3		Daytime n = 7	Nighttime n = 9		Regular hours n = 6	Off hours n = 10	
	Mean ± SD Median (IQR)								
Door-to-needle time, minutes	75 ± 16 75 (23)	82 ± 32 87 (63)	0.60	71 ± 20 75 (35)	81 ± 18 80 (19)	0.34	75 ± 19 76 (25)	77 ± 20 75 (25)	0.83
Stroke onset to treatment time, hours	3.0 ± 1.1 2.7 (0.4)	3.0 ± 0.6 2.9 (1.2)	0.59‡	3.3 ± 1.4 2.9 (0.5)	2.8 ± 0.5 2.7 (0.5)	0.29‡	3.4 ± 1.5 2.8 (0.5)	2.8 ± 0.5 2.7 (0.5)	0.39‡

This analysis was limited to patients treated with intravenous tissue plasminogen activator; †A t-test was used to compare groups, unless otherwise specified; ‡A Mann-Whitney test was performed.

measurements ($p > 0.05$, Figure 3). Patients arriving at the ED from 16:01 to 7:59, for example, had the same median for the door-to-CT-scan time (in minutes) as those arriving from 8:00 to 16:00 (median = 15, IQR = 16 and 15, respectively) did. Those ischemic stroke patients arriving on weekdays or during off hours also had a door-to-CT-scan time median of 15 minutes (IQR = 10 and 16, respectively), whereas patients arriving on a weekend or during regular hours had medians of 18 minutes (IQR = 20) and 13 minutes (IQR = 11), respectively ($p > 0.05$). Patients with the time recorded from door-to-CT-scan were similar (regarding age and sex) to those patients without the time recorded; however, the mean of stroke severity proved to be significantly higher for those with the time recorded from door-to-CT-scan than it was for their counterparts (10 ± 6 vs. 6 ± 4 ; $p = 0.03$).

Discussion

The purpose of this study was to evaluate the association between measures of patient arrival time (day, day part and hour) at the Emergency Department of the Puerto

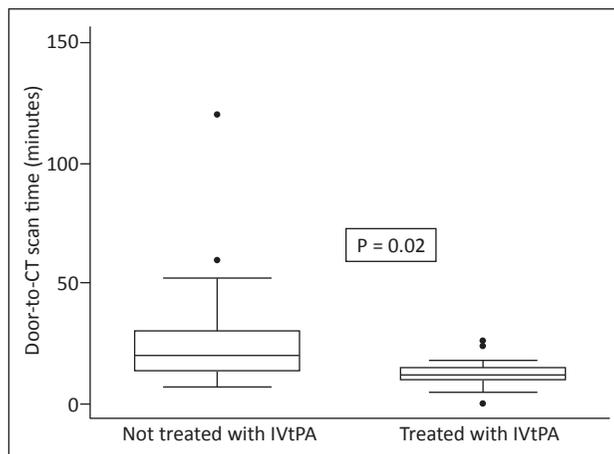


Figure 2. Door-to-CT scan time (in minutes) box plots for patients treated/not treated with intravenous tissue plasminogen activator (IVtPA). Differences between exposure measurements were assessed using the Mann-Whitney test.

Rico Medical Center with measures of the timeliness of stroke management interventions (door-to-CT-scan, door-to-needle, and stroke onset-to-treatment) at the SU. There were no statistically significant associations between the 3 different measures of patient arrival time (exposures) and the measures of timeliness of stroke management interventions (outcomes). Thus, we did not observe a

weekend effect with regard to stroke management interventions in this group of ischemic stroke patients.

Our results show that most of the patients treated with IVtPA arrived during off hours, even if their arrival was on a weekday, a finding which is similar to what has already been reported in the literature (17). Our data are also consistent with studies proposing that the weekend effect is not present in fully staffed academic medical centers (18), where disparities in staffing, resources and expertise might not be reduced, as has been reported as being the case at other clinical sites (15). Albright suggests that the weekend effect can be minimized by establishing comprehensive stroke centers with dedicated stroke teams composed of stroke physicians and expert nursing staff, following established evidenced-based protocols (18). The fact that the SU, is an emerging comprehensive stroke center located within the principal medical center of the island might explain, in part, the absence of the weekend effect in terms of door-to-CT-scan time, door-to-needle-time, and onset-to-treatment-time in this study.

All the IVtPA-treated, ischemic stroke patients received the treatment beyond the 60-minute door-to-needle time goal (19). One determinant that has been proposed in the literature to explain door-to-needle time delay is the arrival of the patient at the ED within an hour of symptom onset, independent of severity (11). This early arrival seems to produce a relaxed, “time is on our side” perception (11). There is not a specific determinant identified that precludes door-to-needle time-goal achievement. Treatment initiation and door-to-needle time delay occurs in patients arriving early after symptom onset (11). In our study, the differences between the door-to-needle times of each time group are not statistically significant and may be unrelated to the finding of door-to-needle times exceeding the 60-minute goal.

Ever since the European Cooperative Acute Stroke Study (ECASS III) published its findings, an increase in the use of IVtPA has been noted and median door-to-needle has decreased (20). Still, door-to-needle times of less than or equal to 60 minutes have been achieved in a third or fewer of the treated patients (9,19). In US hospitals, Hispanics are more likely to have door-to-needle times of greater than 60 minutes than non-Hispanic whites are (19). In our study, the mean and SD for door-to-needle time was

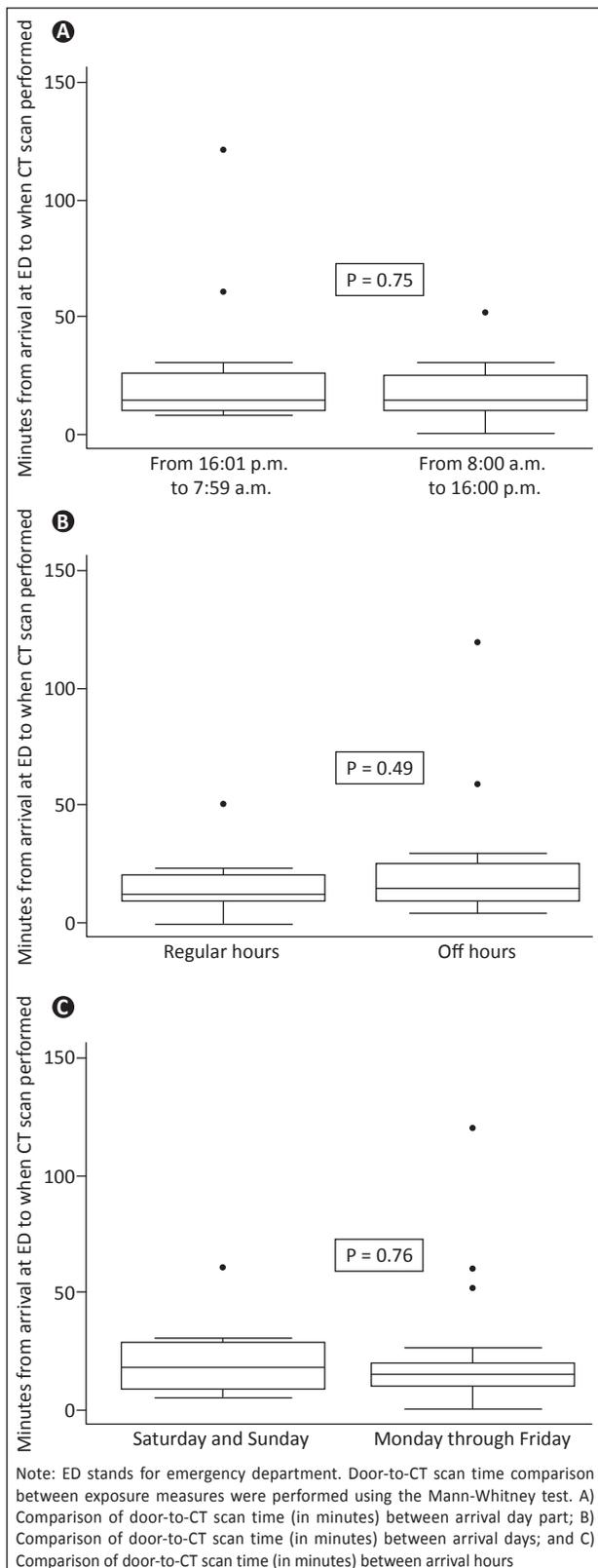


Figure 3. Box plots characterizing door-to-CT scan time (in minutes) of ischemic stroke patients by arrival day part (A), day (B), and hour designation (C) (n = 34). Differences between exposure measurements were assessed using the Mann-Whitney test.

77 ± 18 minutes. Thus, our study indicates that door-to-needle times at the SU should continue to improve (that is, decrease) with the increased implementation of stroke protocols.

An expanded window of treatment (4.5 hours) will not benefit many patients, primarily because the more restricted exclusion criteria will disqualify many of those who arrive after the standard 3-hour window has closed (21). This, in fact, might have been what occurred here, as only 16 (30%) out of the 54 participants in our study ended up being treated with IVtPA. Onset-to-arrival time is influenced mainly by stroke severity and arrival mode (11). Public stroke awareness and rapid response to symptoms, EMS notifications, and transportation to experienced centers, as well as physician/team responses to the urgency of timeliness of treatment, are factors that should improve door-to-needle times (21).

This study has several limitations. Because of the pre-existing nature of our database, created for quality improvement purposes, we did not have information on stroke risk factors, which could have influenced both the arrival time and the outcomes. Hence, we cannot exclude the possibility of residual confounding by these factors. Another limitation is that the sample size for this analysis was small, therefore hindering the performing of more advanced statistical analyses and possibly affecting the statistical significance of the results. The stroke unit of the Puerto Rico Medical Center is an academically oriented tertiary care unit serving mainly the San Juan Metropolitan area, and therefore our findings may not be generalizable to the timeliness of stroke management interventions in other parts of the island.

This study also has several strengths. During the study period, the stroke unit was the preeminent stroke center on the island and the site of the initiation of the implementation of the Get With The Guidelines program. Ours is the first study to focus on the accomplishment of stroke management interventions and the timeliness of those interventions offered to patients at the stroke unit of the Puerto Rico Medical Center. The high quality nature of the data recorded using the Get With The Guidelines-Stroke Patient Management Tool facilitates research and promotes enhanced quality of care.

In conclusion, this study demonstrates that ischemic stroke patients receiving medical care at the Puerto Rico Medical Center stroke unit within the period covering from August 2008 through February 2010 were treated in the same manner, regardless of a given patient's time of arrival at the Emergency Department. Consequently, the data suggest that there is no weekend effect, at least not regarding stroke management interventions, taking place at the stroke unit. Critical ischemic stroke management interventions occur within the established standard of care for IVtPA-eligible patients. Attainment of the previously mentioned door-to-needle time goal is achievable. The stroke unit accomplished the door-to-CT-scan time goal and the onset-to-treatment time standard. Since the door-to-needle times were over the 60-minute goal, there is a need to continue with the implementation of quality improvement measures to bring door-to-needle times down to the desired goal.

Resumen

Objetivo: Evaluar la asociación entre medidas de tiempos de llegada del paciente al Departamento de Emergencia del Centro Médico de Puerto Rico y las medidas de puntualidad del manejo de intervenciones en pacientes con eventos cerebrovasculares isquémicos en la Unidad Cerebrovascular. **Métodos:** En este estudio retrospectivo, información de 54 pacientes se obtuvo de la Unidad de Cerebrovascular del Centro Médico de Puerto Rico a través del “Get With The Guidelines-Stroke Registry”. Fueron incluidos pacientes con eventos cerebrovasculares isquémicos, quienes tenían mínimo 18 años de edad durante el periodo agosto 2008-febrero 2010. Las asociaciones entre medidas de tiempos de llegada del paciente y las medidas de puntualidad del manejo de intervenciones en pacientes se evaluaron usando: prueba de t/Mann-Whitney y prueba de ji-cuadrado/Exacta de Fisher, según fuera apropiado. **Resultados:** La mayoría de los pacientes fueron hombres (74%). La media y desviación estándar de la edad fue 67±14 años. La mediana del tiempo desde puerta-a-CT-scan e inicio de síntomas-a-tratamiento fue 15 minutos (rango intercuartil=15) y 2.7 horas (rango intercuartil=0.6), respectivamente. La media y desviación estándar del tiempo desde la puerta-a-aguja fue 77±18 minutos. No hubo diferencias para ninguna de las variables según el tiempo de llegada del paciente ($p>0.05$). La mediana del tiempo desde la puerta-a-CT-scan fue más corto para pacientes que recibieron tratamiento comparado a los que no recibieron tratamiento (12 minutos vs. 20 minutos, $p=0.02$). **Conclusiones:** La puntualidad del manejo de intervenciones para eventos cerebrovasculares isquémicos no difirió según día de llegada, parte del día u hora del día.

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References

- Go A, Mozaffarian D, Roger V, Benjamin E, Berry J, Blaha M, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014;129:339–410.
- Zevallos J, Santiago F, Gonzalez J, Rodriguez A, Pericchi L, Rodríguez-Mercado R, Nobo U. Burden of stroke in Puerto Rico. *International Journal of Stroke* 2015;10:117–119.
- Lloyd-Jones D, Adams R, Brown T, Carnethon M, Dai S, De Simone G, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2010 update: A report from the American Heart Association. *Circulation* 2010;121:e46–e215.
- Schwamm L, Reeves M, Pan W, Smith E, Frankel M, Olson D, et al. Race/ethnicity, quality of care, and outcomes in ischemic stroke. *Circulation* 2010;121:1492–1501.
- Schwamm L, Fonarow G, Reeves M, Pan W, Frankel M, Smith E, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation* 2009;119:107–115.
- Hong K, Saver J. Years of disability-adjusted life gained as a result of thrombolytic therapy for acute ischemic stroke. *Stroke* 2010;41:471–477.
- Hacke W, Kaste M, Bluhmki E, Brozman M, D'avalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–1329.
- Lees K, Bluhmki E, Von Kummer R, Brott T, Toni D, Grotta J, et al.; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;375:1695–1703.
- Fonarow G, Smith E, Saver J, Reeves M, Hernandez A, Peterson E, et al. Improving door-to-needle times in acute ischemic stroke: the design and rationale for the American Heart Association/American Stroke Association's target: stroke initiative. *Stroke* 2011;42:2983–2989.
- Minnerup J, Wersching H, Ringelstein E, Schilling M, Schäbitz W, Wellmann J, Berger K. Impact of the extended thrombolysis time window on the proportion of recombinant tissue-type plasminogen activator-treated stroke patients and on door-to-needle time. *Stroke* 2011;42:2838–2843.
- Saver J, Smith E, Fonarow G, Reeves M, Zhao X, Olson D, Schwamm LH; GWTG-Stroke Steering Committee and Investigators. The “Golden Hour” and Acute Brain Ischemia: Presenting Features and Lytic Therapy in >30 000 Patients Arriving Within 60 Minutes of Stroke Onset. *Stroke* 2010;41:1431–1439.
- Hacke W, Furlan A, Al-Rawi Y, Davalos A, Fiebich J, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion--diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2009;8:141–150.
- Adams HP Jr, del Zoppo G, Alberts M, Bhatt D, Brass L, Furlan A, et al.; American Heart Association/American Stroke Association Stroke Council; American Heart Association/American Stroke Association Clinical Cardiology Council; American Heart Association/American Stroke Association Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease Working Group; Quality of Care Outcomes in Research Interdisciplinary Working Group. *Circulation* 2007;115:e478–e534.
- Reeves M, Smith E, Fonarow G, Hernandez A, Pan W, Schwamm L; GWTG-Stroke Steering Committee & Investigators. Off-hour admission and in-hospital stroke case fatality in the get with the guidelines-stroke program. *Stroke* 2009;40:569–576.
- Saposnik G, Baibergenova A, Bayer N, Hachinski V. Weekends: a dangerous time for having a stroke? *Stroke* 2007;38:1211–1215.
- Tung Y, Chang G, Chen Y. Associations of physician volume and weekend admissions with ischemic stroke outcome in Taiwan: a nationwide population-based study. *Med Care* 2009;47:1018–1025.
- Jauss M, Schütz H, Tanislav C, Misselwitz B, Rosenow F. Effect of daytime, weekday and year of admission on outcome in acute ischaemic stroke patients treated with thrombolytic therapy. *Eur J Neurol* 2010;17:555–561.
- Albright K, Raman R, Ernstrom K, Halleli H, Martin-Schild S, Meyer B, et al. Can comprehensive stroke centers erase the ‘weekend effect’? *Cerebrovasc Dis* 2008;27:107–113.
- Fonarow G, Smith E, Saver J, Reeves M, Bhatt D, Grau-Sepulveda M, et al. Timeliness of Tissue-Type Plasminogen Activator Therapy in Acute Ischemic Stroke: Patient Characteristics, Hospital Factors, and Outcomes Associated With Door-to-Needle Times Within 60 Minutes. *Circulation* 2011;123:750–758.
- Messé S, Fonarow G, Smith E, Kaltenbach L, Olson D, Kasner S, Schwamm LH. Use of tissue-type plasminogen activator before and after publication of the European Cooperative Acute Stroke Study III in Get With The Guidelines-Stroke. *Cir Cardiovasc Qual Outcomes* 2012;5:321–326.
- De los Ríos la Rosa F, Khoury J, Kissela B, Flaherty M, Alwell K, Moomaw C, et al. Eligibility for Intravenous Recombinant Tissue-Type Plasminogen Activator Within a Population: The Effect of the European Cooperative Acute Stroke Study (ECASS) III Trial. *Stroke* 2012;43:1591–1595.