

Contribution of Onset-to-Alarm Time to Prehospital Delay in Patients with Ischemic Stroke

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Background: Stroke is a leading cause of death and disability. Tissue plasminogen activator (tPA) improves the clinical outcome when administered properly; however, the most important factor to receive tPA is time. The main reason for late hospital arrival is a considerable delay in onset-to-alarm time (OAT), comprising more than 50% of the onset-to-door time. **Aims:** To identify the factors associated with a delay in OAT and evaluate its contribution to onset-to-door time in ischemic stroke patients. **Methods:** Prospective cohort of stroke patients admitted to the UANL University Hospital. OAT was defined as the time from identification of stroke symptoms to the decision to seek medical attention. **Results:** A total of 189 patients were included. Mean age was 61 ± 13 years, 62% were men. One-hundred and one patients had a short OAT, but only 20.9% arrived during the first 3 hours after stroke onset. Being employed ($P = 0032$; odds ratio [OR] 2.784, 95% confidence interval [CI] 1.091-7.104), attributing symptoms to stroke ($P = 0016$; OR 3.348, 95% CI 1.254-8.936), and perceiving stroke symptoms as severe ($P = 0031$; OR 2.428, 95% CI 1.083-5.445) were associated with a shorter OAT. **Conclusions:** OAT consumes a considerable amount of the onset-to-door time. It is necessary to increase stroke knowledge and emphasize the severity of stroke, regardless of the severity of its clinical manifestations to reduce the prehospital delay, especially in countries with limited access to treatment with an extended time frame.

Key Words: Prehospital delay—onset-to-alarm—onset-to-door—ischemic stroke—rtPA

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Introduction

Cardiovascular diseases, including stroke, will increase 60% from 2000 to 2020 in developing countries, compared

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to a 5% increase in developed countries.¹ The Latin American population has gone through an epidemiologic transition, which led to an increase in cardiovascular risk factors and a greater risk for stroke.²

Globally, stroke is the second cause of death and the first cause of disability,³ with a higher incidence in low- and middle-income countries.⁴ In Mexico, statistics are concordant with those reported worldwide⁵ and are related to the aging of the population along with a higher prevalence of cardiovascular risk factors; for instance, hypertension, diabetes, and dyslipidemia.⁶

Reperfusion therapy using tissue plasminogen activator (tPA) is the treatment of choice in ischemic stroke and improves the clinical outcome when administered properly; however, the most important factor to receive tPA is time.⁷ Notwithstanding, in multicenter series, less than 30% of patients arrive in a timely fashion to receive tPA,⁸ with similar results in Mexico.⁹ Onset-to-door time (OTD) could be divided in *onset-to-alarm time* (OAT) that starts with the identification of stroke symptoms and ends with

the decision to seek medical attention, and *transfer time*, which corresponds to the elapsed time to arrive to the hospital. It has been reported that the main reason for a late hospital arrival is a considerable delay in OAT, comprising more than 50% of the OTD.¹⁰ Limb weakness altered speech and duration of symptoms for more than 10 minutes associate with a reduction in OTD,¹¹ while considering stroke symptoms as severe, being in a public place and not going to a primary care physician relate with a shorter OAT.¹² However, the factors associated with OAT are diverse and vary depending on the population.

Aims

To identify the factors associated with a delay in OAT and to evaluate its contribution to the OTD in patients with ischemic stroke.

Materials and Methods

A prospective, observational study of a consecutive sample was performed at the Department of Neurology of the University Hospital (UANL) in Monterrey, Mexico. Clinical and demographical data were obtained using a standardized data capture from a stroke registry (iReNe).¹³ All patients diagnosed with ischemic stroke who were ≥ 18 years and admitted between January and December 2018 were recruited. Ischemic stroke was confirmed by neuroimaging. Data included sociodemographic information, cardiovascular risk factors, stroke onset, and number of medical consultations prior to the arrival to our center. Patients were classified as having diabetes mellitus or hypertension if they self-reported a prior diagnosis or were using antidiabetic or antihypertensive drugs. Sedentarism was defined as the lack of aerobic exercise for at least 30 minutes, 3 times a week. Information at the time of symptom onset included the number of people present at stroke onset, who identified the stroke symptoms, what the first action was after stroke was identified, and if symptoms were interpreted as severe, as reported previously.^{14,15} OAT was defined as the time from when the patient/witness identified the symptoms of stroke until a decision to seek medical attention was made.

This study was authorized by the Research and Ethics Committee (NR18-0002). All patients provided verbal informed consent before the enrollment of their data in iReNe.

For the analysis, participants were divided in 2 groups, short OAT, defined as 30 minutes or less, and long OAT (>30 minutes). A threshold was established in order to have a considerable amount of time available to arrive to the hospital and receive proper attention by stroke specialists. Categorical variables were analyzed using χ^2 and Fisher's exact test; continuous variables were analyzed using the Mann-Whitney *U* Test or Student's *t* test. Results are presented as percentages, means \pm standard deviation

(SD) or as medians with their corresponding interquartile range (IQR). *P* values < 0.05 were considered statistically significant. A logistic regression adjusted for sex and age was performed including previously reported variables associated with OAT and a *P* < 0.1 after a univariate analysis to identify the variables related with shorter OAT. The statistical analysis was performed using SPSS v.25.

Results

A total of 189 patients were admitted during the study period. Twenty-six cases were excluded because the OAT could not be determined precisely. Characteristics of the population are shown in Table 1. Mean age was 61 ± 13 years and the majority of patients were men (62%). Years of education were 7.17 ± 4.17 and the median number of people with whom the patient lived was 2.¹⁻⁴ The most common cardiovascular risk factors were sedentarism (79.1%), hypertension (61.3%), and diabetes (46%). Patients did not have a previous disability measured by the Rankin and Barthel scale.

At the time of the event, patients were at home (78.5%) or in a public place (13.5%), with a small number being at work (5.5%). Patients were with at least 1 companion, median 1 (IQR: 1-3), and went to a health care service before arriving at a comprehensive stroke center, median 1 (IQR: 0-1). Only 22.1% attributed their symptoms to a stroke. When asked what the first action was after the stroke symptoms 12.3% activated the emergency medical services (EMS), and 26.4% preferred to wait for spontaneous recovery. Most of the patients arrived at our Stroke Center by their own car (65.6%), and 22.7% were transferred by ambulance.

Median OAT at admission was 60 minutes (IQR: 10-380 minutes) and OTD was 649 minutes (IQR: 215-2315 minutes). Almost half of the patients 80 (49.1%) were classified as having a short OAT, and only 30 (37.5%) of them arrived during the first 3 hours after stroke onset. NIHSS and Rankin evaluation at admission were 8.41 ± 5.03 and 3.19 ± 1.27 , respectively. Thrombolysis was administered in 14 (8.9%) patients. The rest of the characteristics of both groups are shown in Table 2.

In a multivariate analysis, the variables that were associated with a shorter OAT were: being employed (*P* = 0.032; odds ratio [OR] 2.784, 95% [confidence interval] CI 1.091-7.104), attributing symptoms to stroke (*P* = 0.016; OR 3.348, 95% CI 1.254-8.936), and perceiving stroke symptoms as severe (*P* = 0.031; OR 2.428, 95% CI 1.083-5.445). Whereas waiting for spontaneous recovery (*P* = 0.003; OR 14.770, 95% CI 2.523-86.485) and attributing symptoms to a disease different than stroke (*P* = 0.043; OR 2.789, 95% CI 1.034-7.526) were associated with a long OAT.

Discussion

We described the factors associated with the OAT in patients with ischemic stroke. Despite the OAT being

Table 1. Characteristics of the participants

Variable	N = 163
Sociodemographic data	
Age \pm SD	60.47 \pm 13.25
Male	101 (62)
Marital status	
Married	92 (56.4)
Single	23 (14.1)
Widowed	19 (11.7)
Years of education	7.17 \pm 4.17
Employee	87 (53.4)
No. of persons with whom patient lives, median (IQR)	2 (1-4)
Cardiovascular risk factors	
Sedentarism	129 (79.1)
Hypertension	100 (61.3)
Diabetes mellitus	75 (46)
Family history of stroke	36 (22.1)
Stroke	28 (17.2)
Myocardial infarction	17 (10.4)
Previous status	
Rankin, median (IQR)	0 (0-0)
Barthel, median (IQR)	100 (100-100)
Information at the time of event	
Number of people present at onset of stroke, median (IQR)	1 (1-3)
Prior consultations, median (IQR)	1 (0-1)
Direct admission to stroke center	55 (34)
Attribution of symptoms to stroke	36 (22.1)
Who recognized the symptoms?	
Patient	80 (49.4)
Witness	82 (50.6)
Where did the stroke onset occur?	
Home	128 (78.5)
Public place	22 (13.5)
Work	9 (5.5)
Perception of symptoms as severe	95 (58.3)
First action after recognition of stroke	
Call 9-1-1	20 (12.3)
Attend to the hospital	86 (52.8)
Wait for recovery	43 (26.4)
Mode of transport to stroke center	
Ambulance	37 (22.7)
Own car	107 (65.6)
Taxi	18 (11)
Evaluation at admission	
NIHSS	8.41 \pm 5.03
Rankin	3.19 \pm 1.27
Wake up stroke	33 (20.2)
Stroke symptoms	
Altered mental status	55 (33.7)
Dysarthria	79 (48.5)
Facial palsy	98 (41.71)
Upper limb weakness	133 (81.59)
Lower limb weakness	131 (80.38)
Onset-to-alarm, min (IQR)	60 (10-360)
Onset-to-door, min (IQR)	649 (215-2315)
OTA/OTD, %	10.30 (1.37-40)

(Continued)

Table 1 (Continued)

Variable	N = 163
OTA	
≥ 30 min	80 (49.1)
> 30 min	83 (50.9)
OTD	
< 180 min	34 (20.9)
≥ 180 min	129 (79.1)
Intravenous thrombolysis	14 (8.9)

considered as the main cause of delay in patients with ischemic stroke,¹⁰ we report that almost half of our population decided to seek medical assistance almost immediately. OTD was considerably long in a significant proportion of patients, sharing similar results with a previous study in our country,⁹ thus deluding patients from thrombolytic therapy. On the other hand, a greater proportion of patients with a short OAT benefited from IV thrombolysis due to a direct and faster admission to our stroke center. Although the difference in thrombolysis did not reach statistical significance ($P = 0.07$) when compared between short and long OAT, we cannot underestimate the relevance of this proportion as the clinical and functional benefits of thrombolysis are clear and for every minute saved from onset-to-treatment an average of 1.8 days of extra healthy life is granted.¹⁶

We found that only 34% of the patients arrived directly to our comprehensive stroke center; therefore, a great number of participants decided to visit first either a general practitioner or a family doctor, increasing the length of the prehospital delay and affecting their functional outcome, as it has been described that direct admission to a stroke center is related with a better functional status at 90 days.¹⁷ As more than half of our population contacted a health care professional, it is of relevance to consider the action or recommendation he or she gave to the patient. In a previous study, 60% of the patients who phoned a general practitioner after stroke onset were asked to go to the office in person, leading to a significant prehospital delay ($P = < 0.001$) and a lower thrombolysis rate ($P = 0.003$).¹⁰ Since a great proportion of stroke patients do not directly attend a stroke center, health care professionals who are considered by the general population as the first option to receive medical assistance need to be trained to immediately refer patients to a comprehensive stroke center and reduce the prehospital delay. Therefore, our results could be used as a reference to health authorities to establish continuing education programs to primary care physicians to act fast when identifying a possible stroke.

In contrast with a study by Nowacki et al,¹⁸ in which only 18.5% of the patients who arrived to the hospital within the first 2 hours of stroke onset attributed their symptoms to stroke, in our study, a greater proportion

Table 2. Characteristics of the participants depending on the onset-to-alarm delay

Variable	Short OAT, N = 80	Long OAT, N = 83	P value
Sociodemographic data			
Age \pm SD	60.96 \pm 14.64	59.99 \pm 11.84	0.640
Male	47 (58.8)	54 (65.1)	0.407
Marital status			
Married	45 (56.3)	47 (56.6)	0.672
Single	12 (15)	11 (13.3)	
Widowed	9 (11.3)	10 (12)	
Years of education	6.78 \pm 4.04	7.53 \pm 4.27	0.247
Employee	35 (43.8)	52 (62.7)	0.016*
No. of persons with whom the patient live, median (IQR)	3 (1-4)	2 (1-4)	0.113
Cardiovascular risk factors			
Sedentarism	63 (78.8)	66 (79.5)	0.904
Hypertension	45 (56.3)	55 (66.3)	0.189
Diabetes mellitus	28 (35)	47 (56.6)	0.015*
Family history of stroke	20 (25)	16 (19.3)	0.313
Stroke	16 (20)	12 (14.5)	0.410
Myocardial infarction	12 (11.9)	5 (8.1)	0.396
Previous status			
Rankin, median (IQR)	0 (0-0)	0 (0-0)	0.379
Barthel, median (IQR)	100 (100-100)	100 (100-100)	0.222
Evaluation at admission			
NIHSS	9.01 \pm 5.46	7.81 \pm 4.51	0.192
Rankin	3.16 \pm 1.41	3.22 \pm 1.12	0.834
Information at the time of event			
Number of people present at onset of stroke, median (IQR)	2 (1-3)	1 (1-3)	0.245
Prior consultations, median (IQR)	1 (0-1)	1 (0-1)	0.033*
Direct admission to stroke center	33 (41.3)	22 (26.5)	0.04*
Where did the stroke onset occur?			
Home	66 (82.5)	62 (74.7)	0.082
Public place	12 (15)	9 (14.5)	
Work	1 (1.3)	8 (12.9)	
Attribution of symptoms to stroke	25 (31.3)	11 (13.3)	0.011*
Who recognized the symptoms?			
Patient	37 (46.8)	43 (51.8)	0.527
Witness	42 (53.8)	40 (48.2)	
Perception of symptoms as severe	57 (71.3)	38 (45.8)	0.001*
First action after recognition of stroke			
Call 9-1-1	18 (23.1)	2 (2.4)	<0.001*
Attend to the hospital	48 (61.5)	38 (45.8)	
Wait for recovery	5 (6.4)	38 (45.8)	
Other	7 (9)	4 (4.8)	
Mode of transport to Stroke Center			
Ambulance	23 (28.7)	14 (16.9)	0.147
Own car	51 (63.7)	56 (67.5)	
Taxi	6 (7.5)	12 (14.5)	
Wake up stroke	16 (20)	17 (20.5)	0.919
Stroke symptoms			
Altered mental status	37 (32.5)	29 (34.9)	0.787
Dysarthria	37 (46.3)	42 (50.6)	0.632
Facial palsy	51 (63.7)	47 (56.6)	0.295
Upper limb weakness	65 (81.3)	67 (80.7)	0.787
Lower limb weakness	64 (80)	64 (77.1)	0.527
Onset-to-door, min (IQR)	275.5 (135-873.75)	1440 (570-3271)	<0.001*
OTA/OTD, %	1.6 (0-8.35)	33.3 (11.1-70.9)	<0.001*

Table 2 (Continued)

Variable	Short OAT, N = 80	Long OAT, N = 83	P value
OTD			<0.001*
<180 min	30 (37.5)	4 (4.8)	
≥180 min	50 (62.5)	79 (95.2)	
Intravenous thrombolysis	10 (13)	4 (4.9)	0.075

* Represents a *p* value < 0.05.

(31.3%) of those with a short OAT thought they were having a stroke. However, the number of patients able to attribute their symptoms to stroke dropped to 22.1% when taking into account those with a short and long OAT. These results are alarming and concordant even with developed countries in which less than 50% of a representative sample from European countries associated the most common stroke signs to stroke.¹⁹ Therefore, a special consideration should be taken in this point of pre-hospital delay, as the correct interpretation of symptoms relates to a faster decision to seek medical help and an earlier hospital arrival.^{20,21} Further educational campaigns targeted to specific groups, such as those in moderate to greater risk of having a stroke, should be developed in order to increase stroke knowledge and correctly attribute symptoms to stroke.

In a previous study, perception of stroke symptoms as severe was the only variable associated with a faster decision to seek medical assistance.²² Interestingly, in the present study, it remained significant. Also, De Silva et al,²³ found similar results, as they compared the timing of arrival to a tertiary care hospital in 2004 and 2009 and reported that the only reasons that were associated with a delayed arrival in both years were failure to recognize symptoms of stroke and not recognizing the severity of symptoms. Perception of stroke symptoms as severe is associated with a shorter pre-hospital delay, regardless of their attribution,^{15,24,25} and it is of relevance as the most common manifestations of stroke are not as shocking as symptoms of an acute myocardial infarction or acute abdomen.

Being employed was associated with a faster decision to seek medical attention. A possible explanation for this finding is mentioned in a qualitative study by Moloczij et al, who reported that losing the “sense of normality”, referred as not being able to maintain work or family commitments, contributes to a faster decision to seek medical attention.²⁶ However, results evaluating employment and its association with hospital arrival in stroke patients remain inconsistent.²⁷ Further research in the role of employment and the decision to look for medical attention in stroke is needed to address this finding.

Activation of EMS is related with an earlier hospital arrival,²⁸ however, in our study, only 12.3% of patients activated the EMS, while 26.4% decided to wait for spontaneous recovery. A greater number of patients (23.1%) decided to call an ambulance (9-1-1) in the short OAT group, however this result contrasts with those of different countries where

up to 76% of participants' first action would be to call an ambulance after recognizing a stroke.^{19,29} The emergency number 911 was implemented in Mexico in 2017 and an intense advertising campaign has been promoted since its introduction. Furthermore, 911 serves not only as a referral for an ambulance but also for medical advice, therefore, there might be patients who received medical assistance by phone and decided to go to the hospital by their own means. Greater efforts need to be done in order to decrease the number of patients or witnesses who decide to wait for spontaneous recovery and increase the number of those who use 9-1-1. An unexpected finding was the lack of association between stroke severity and a faster decision to seek medical assistance, as described in previous studies.^{30,31} We believe these results could be explained by the limited stroke awareness in our population.³²

Our study presented limitations: stroke knowledge was not evaluated, which could be a determining factor to seek medical assistance, and our results are limited to 1 stroke center. It would be beneficial to compare our results with more stroke centers. Some strengths of the present study are the consecutive sample and the complete information of the prehospital time, which led us to have a clearer panorama of the reasons for a delayed arrival to the hospital.

Conclusions

Onset-to-alarm is determinant for timely hospital arrival in ischemic stroke, as it consumes a considerable amount of the OTD. It is necessary to increase stroke knowledge and make a special emphasis on stroke severity. Fostering stroke awareness and correct interpretation of symptoms are needed to increase the number of patients receiving intravenous thrombolysis, especially in countries with limited access to treatments with an extended time frame.

Declaration of Competing Interest

The authors report no conflicts of interests.

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