



Research Paper: Symptom-to-needle Times in Acute Ischemic Stroke and Its Prehospital Related Factors



Mozaffar Hosseininezhad¹, Rasoul Tabari-Khomeian², Yaser Moaddabi¹, Amirreza Ghayeghran¹, Sedighe Esmailzade³, Maryam Ghasemi⁴, Seyyed Mahdi Zia Ziabari^{4*}, Fatemeh Shafaei

1. Department of Neurology, School of Medicine, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran
2. Social Determinants of Health Research Center; Guilan University of Medical Sciences, Rasht, Iran
3. General Physician, Guilan University of Medical Sciences, Rasht, Iran
4. Department of Emergency Medicine, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
5. Poursina hospital, Guilan university of Medical Sciences, Rasht, Iran

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Running Title Delay in CVA Management and Prehospital Factors

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ABSTRACT

Background: Intravenous (IV) recombinant tissue Plasminogen Activator (rtPA) (IV-rtPA) is the only FDA-approved pharmacological therapy for treatment in acute ischemic stroke and the administration of IV-rtPA is crucially time-dependent.

Objectives: This study aimed to evaluate symptom-to-needle time and factors associated with the prehospital delay in patients with acute ischemic stroke referred to Poursina Hospital, a referral hospital in the north of Iran.

Materials & Methods: In this cross-sectional study, all patients with acute stroke referred to Poursina Hospital from June to December 2016 were evaluated. The study data were extracted from the patients' records. SPSS v. 21 was used to analyze the obtained data. The independent samples t test and the Chi-square test were used to explore the appropriate relation of variables.

Results: A total of 322 patients were included. Their mean age was 74.4 years and 55.6% were male. According to findings, only 74 patients (22.98%) were transferred to the hospital via Emergency Medical Service (EMS), most of them (64.86%) arrived at the right time. There is a significant relationship between EMS transfer use and arriving at the hospital at the right time. Overall, 13.9% of patients received IV rtPA, and 75.5% of the patients received rtPA in less than 60 minutes. Among the patients arrived in the golden time, the average times to treatment were as follows: onset-to-door (OTD), 105 min; door-to-admission, 3 min; admission-to-doctor, 7 min; doctor-to-Computed Tomography (CT), 15 min; CT-to-treatment, 26 min; symptom to needle time, 152 min; and door-to-needle time (DNT), 49 min.

Conclusion: According to this study, although the two-third of eligible patients were transferred to the hospital at the right time, the rate of using EMS for patient transportation is low.

Keywords: Stroke, Tissue plasminogen activator, Patient care

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* Corresponding Author:

Seyyed Mahdi Zia Ziabari

Address: Department of Emergency Medicine, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

Tel: +98 (911) 1375056, **Fax:** +98 (13) 44553184

E-mail: smz102186@gmail.com

Highlights

- A small number of patients have been transferred to the referral center for cardiovascular accidents via emergency medical service.
- Only 8.87% of patients who did not use emergency medical service had reached the hospital at the right time, compared to 64.86% who were transferred by emergency medical service.
- Most patients who were referred by emergency medical service received the intravenous recombinant tissue plasminogen activator at the right time.

Introduction

Intravenous (IV) recombinant tissue Plasminogen Activator (rtPA) is the only Food and Drug Administration (FDA) approved pharmacological therapy for the treatment of Acute Ischemic Stroke (AIS) [1]. Only small proportions of patients with ischemic stroke receive IV-rtPA, in most centers. The most important factor limiting intravenous rtPA administration is the time because it needs to be administered within 4.5 hours of symptom onset. The clinical benefit of intravenous rtPA diminishes rapidly even during the golden time [2]. Even for the patients arriving in golden time, the administration of rtPA is not always done. Also, the contraindications for administering intravenous thrombolytic should be identified [3].

National guidelines have supported the rapid evaluation and treatment of patients with AIS. National Institute of Neurological Disorder timeline targets for attaining CT scan in 20 minutes to start rtPA infusion in 60 minutes of arrival to the Emergency Department. Currently, most hospitals struggle to have half of their AIS patients meet these targets [4].

In Iran, there has been an improvement in stroke management. However, reports suggest that the administration of IV-rtPA in Iran is lower than in many other countries [5]. Therefore, the Iranian Ministry of Health has recently announced that the prevention and treatment of stroke is a national health priority [6].

This study aims to evaluate symptom to needle time and factors associated with the prehospital delay in patients with acute ischemic stroke referred to Poursina Hospital, the only stroke specialist center in the city of Rasht, northern of Iran.

Patients and Methods

In this cross-sectional study, all patients with AIS referred to Poursina Hospital, a referral hospital in the

north of Iran from June to December 2016, were evaluated. The patients' data were collected via a checklist, including demographic information (age, sex), education, occupation, place of residence, patient's companion degree and education, chief complaints, precise onset time of symptoms, use of Emergency Medical Service (EMS), exact Emergency Department (ED) arrival time, admission time, first visit time by the physician, Computed Tomography (CT) time, and rtPA time.

The patients were divided into two groups based on their arrival at the ED within the therapeutic window (non-delayed) or arrival after that time (delayed). Outcome measures were mean symptom-to-door, door-to-admission, admission-to-doctor, doctor-to-CT, CT-to-treatment, door-to-needle, and symptom-to-needle times and determining factors associated with prehospital delays in treating acute stroke.

Patients with missing data, referred from another hospital, or with severe conditions who died before treatment were excluded. Statistical analyses were performed in SPSS v. 21. For continuous variables, Means \pm SD were calculated for normally distributed data. Data were analyzed using t test or Mann-Whitney U test as deemed appropriate and the Chi-square test for categorical parameters. A P-value of less than 0.05 indicated statistical significance.

Results

A total of 530 patients with ischemic stroke were admitted during the study period. However, 208 patients were excluded due to incomplete data. Among 322 remaining patients, 179 patients (55.6%) were men and 143 (44.4%) were women. Their Mean \pm SD of age was 74.7 \pm 8.85 years. About 32.3% of patients were housewives, 21.1% unemployed, and 39.4% were uneducated. Also, 93.8% of the patients' companions were first-degree relatives and 37.3% of them had a diploma. About 34.5% of patients presented with paresis and 21.4% and 15.8% pre-

Table 1. Comparing demographic characteristics of subjects in non-delayed and delayed groups

Characteristics		Non-delayed (n=70)	Delayed (n=252)	P
Age (y), Mean±SD		70.9±11.9	75.85±7.47	<0.001
Male sex, No. (%)		35 (50)	144 (57)	0.341
Job, No. (%)	Self-employed	6 (8.5)	24 (9.5)	<0.001
	Employee	12 (17.14)	0	
	Unemployed	8 (11.4)	60 (23.8)	
	Housewives	20 (28.5)	84 (33.33)	
	Manual worker	7 (10)	60 (23.8)	
Education, No. (%)	Illiterate	19 (27.14)	108 (42.85)	<0.001
	<Diploma	16 (22.85)	96 (38)	
	Diploma	21 (30)	48 (19)	
	University	14 (20)	0	
Place of residence, No. (%)	Rasht	42 (60)	60 (23.8)	<0.001
	Suburb of Rasht	5 (7.1)	48 (19)	
	Other cities	19 (27.14)	36 (14.28)	
	Villages	4 (5.71)	108 (42.85)	
Symptoms, No. (%)	Paresis	39 (55.7)	72 (28.57)	<0.001
	Paresthesia	9 (12.85)	60 (23.8)	
	Speech disorder	12 (17.14)	0	
	Facial asymmetry	3 (4.28)	48 (68.57)	
	Headache	3 (4.28)	24 (9.52)	
	Balance disorder	4 (5.71)	48 (19)	
EMS use, No. (%)		48 (68.57)	26 (10.31)	<0.001


Table 2. Relationship between methods of transportation and the time of arrival to the hospital

Mode of Transportation	Time of Arrival		Total
	Early	Late	
EMS	48 (64.86)	26 (35.14)	74 (100)
Non-EMS	22 (9.73)	226 (90.27)	248 (100)
Total	70 (21.74)	252 (78.26)	322 (100)



sented with paresthesia and facial paresis, respectively. Besides, 31.67% of the patients lived in Rasht City and 22.9% of the patients came to ED using EMS (Table 1).

EMS was used more in the non-delayed group. According to the findings of 322 patients, only 74 (22.98%) were transferred to the hospital via EMS. Most of these patients (64.86%) were taken to the hospital at the right

time and received the necessary medical care. On the other hand, of 248 patients who were transferred to the hospital with other methods of transportation, only 22 patients (8.87%) had reached the hospital at the right time. Statistical analysis showed a significant relationship between ambulance use and arriving at to hospital at the right time ($P<0.001$) (Table 2). Furthermore, results

Table 3. Descriptive statistics of times (in minutes) spent on patients who received IV-rtPA

Variables	No.	Min	Max	Mean±SD
Onset-to-doctor	45	0:15	3:45	1:42±0:46
Door-to-admission	45	0:01	0:10	0:03±0:02
Admission-to-doctor	45	0:01	0:50	0:07±0:08
Doctor-to-CT	45	0:05	0:40	0:15±0:08
CT-to-treatment	45	0:05	1:30	0:26±0:17
Door-to-needle	45	0:15	2:05	0:49±0:23
Symptom-to-needle	45	0:50	4:30	2:32±0:46

IV-rtPA, Intravenous recombinant tissue plasminogen activator; CT, computer tomography.



indicated patients with higher educational levels and with home addresses closer to ED tend to arrive earlier.

Among 322 patients, only 70 patients (21.7%) arrived at the appropriate time, and of those, 45 patients (overall: 13.9%) received intravenous rtPA. Out of 25 patients arrived within the therapeutic window and did not receive rtPA, 5 patients were diagnosed with TIA, 10 patients were diagnosed with ICH; 3 patients used warfarin, 4 patients had a history of the previous stroke, and 3 patients had systolic blood pressure higher than 185 mm Hg.

We evaluated symptom to needle time in the 45 patients received rtPA. The mean onset-to-door OTD time was 105±46 (range: 15-225 min) min. The mean door-to-admission time was 3±2 (range: 1-10 min) min. The mean admission-to-doctor time was 7±8 (range: 1-50 min) min.

The mean doctor-to-CT time was 15±8 (range: 5-40) min. The mean CT-to-treatment time was 26±17 (range: 5-90 min) min. The mean door-to-treatment time was 49±23 (range: 15-125 min) min. The mean symptom-to-needle time was 152±46 (range: 50-270 min) min (Table 3).

Discussion

Reports from Iran suggested that less than 30% of the stroke patients arrive at the hospital within 3 hours of onset and about 40% of the patients are not admitted to the ED on the day of symptom onset [6]. Some reports from other countries showed that 26% to 28% of the patients arrive at the ED within 2 hours of onset; nevertheless, these timings have been analyzed by different methods [7-9]. Our study showed that 70 of 322 patients (21.7%) arrived within the therapeutic window and 13.9% of patients were treated with IV rtPA, which is compatible with other studies in Iran but lower than times found in other

developed countries [3, 10]. Nikkhah et al. in a study in Mashhad, Iran, on AIS patients, reported that 14.3% of the patients were admitted within the therapeutic window and only 1.2% of patients received IV-rtPA. In comparison with this study, our result is much better and a higher percentage of patients were treated with IV-rtPA [5].

The sex ratio and the mean age was similar to other studies, and we did not observe differences in sex between the two groups [3, 5, 10, 11]. In this study, 34.5%, 21.4%, and 15.8% of the patients presented with paresis, paresthesia, and facial paresis, respectively. All patients with speech disturbances arrived within the therapeutic window. On the other hand, 94% of patients with facial paresis, 92% of patients with a balance disorder, and 88% of patients with headache were in the delayed group. The reason for this delay might be due to a lack of understanding of symptom seriousness. Moreover, misinterpreting stroke symptoms can delay ED arrival [7, 12, 13].

A lower proportion of patients arrived by EMS were in the delayed group than the non-delayed group, as EMS decreases the prehospital delay by hastening the transportation and triage processes [7, 8, 14]. These results are consistent with that of Dae-Hyun Kim et al. who investigated whether EMS use and prehospital notification can shorten the time to thrombolytic therapy in a stroke. In their study, 78.5% were transported to the hospital via EMS. The patients who used EMS had shorter median onset-to-arrival time. They also showed that pre-notification by EMS was associated with shorter median door-to-imaging and door-to-needle times (DNT) [15].

Our study indicates that patients with higher levels of education arrive sooner at the hospital which is similar to other study results [16]. But Kim and colleagues showed no difference in education levels [7]. The present study

showed that the longer distance to the ED, the more delay in presentation to ED, which is compatible with other reports [3]. This study indicates that unemployed status predicts delays in the presentation which is to a large extent similar to previous investigations [17].

According to Guidelines of Acute Ischemic Stroke, the conventional goal is to begin physician evaluation in less than 10 minutes, obtain CT in 20 minutes and commence rtPA infusion in 60 minutes of arrival to the ED [4].

In this study, the mean door-to-doctor time was 10 ± 11 min, and the Mean \pm SD doctor-to-CT time was 15 ± 8 min. As mentioned, the mean DNT was 49 ± 23 min and 75.5% of the patients received rtPA in less than 60 min. In Nikkhah et al.'s study in Mashhad, the Mean \pm SD OTD time and to be visited by the on-call neurologist were 113.2 ± 21.3 and 19.3 ± 4.3 min, respectively. The Mean \pm SD door-to-CT scan time was 14.3 ± 5.1 min and the Mean \pm SD onset-to-needle and DNT were 172.1 ± 13.1 and 57.6 ± 8.2 min, respectively [5]. In comparison to this study, our timing is better which led to a higher percentage of patients receiving intravenous thrombolytic.

In a study in Egypt, only 5.8% of those who were eligible for receiving intravenous thrombolysis received intravenous rtPA which is to a large extent lower than our study results. Their study showed that the Mean \pm SD onset-to-arrival time was 147.2 ± 42.5 min and the Mean \pm SD DNT was 87.5 ± 16.4 min [18]. In comparison with the current study, they had a better arrival time even though our DNT is much better.

One study in Taiwan on patients with AIS reported that 21.8% of the patients arrived at the ED within 3 hours of stroke onset, and 5.2% received intravenous thrombolytic. Stroke code improved the number and frequency of IV-tPA treatments for patients with an OTD time of fewer than 3 hours and the efficiency of IV-tPA administration. The median DNT decreased and the percentage of DNT of less than 60 min increased [19]. Their study showed the importance of stroke code in stroke centers.

A prospective study was conducted in the United Kingdom for over 4 years, including 10556 patients. Overall, 11.4% of patients were treated with IVT and the median DNT was 54 min with 61% treated in less than 60 min from arrival at the hospital [20]. In comparison with this study, our numbers are greater. Another study in India was conducted on patients with AIS; 31.87% of patients underwent intravenous thrombolytic therapy. About 23.81% of patients had OTD of 2 h or less, 33.86% had 2-3 hours, 42.33% had 3-4.5 hours, and the median DNT was 63 min

[21]. The IVT rate was higher than this study which could be due to the earlier arrival of the patients to ED.

Our result demonstrated that the most important factors limiting IVT administration in our center are prehospital factors, including patient education, occupation, place of residence, and use of EMS. This result is in line with the work of Wafkin and colleagues who reported that the main causes of prehospital onset-to-arrival delay were stroke unawareness, long travel time, incorrect beliefs, non-available neurologists, stroke onset during sleep. Also, the causes of in-hospital delays include prolonged DNT, financial restraints, minor strokes, unavailable beds, and fear of complications [18].

Based on the previous studies, the administration of rtPA in Iran is lower than that in most developed countries but similar to other developing countries [5] which could be due to the significantly lower rate of early presentation to ED in Iran. The causes of this delay could be limited public knowledge of stroke symptoms, challenging transport of the patients to ED, lack of adequate facilities, and trained personnel for AIS in small cities. Although our in-hospital timing was acceptable, Shahjoui et al. in their study in Iran, showed that improper triage, late imaging or laboratory evaluation, lack of resources in ED were factors limiting intravenous thrombolytic [6].

This study has some limitations. Some data were collected retrospectively. This study was conducted in a single medical center with a small sample size, physicians trained in stroke management, and 24-h neurology resident coverage. Thus, the generalizability of the findings may be limited. Only the frequency of each factor delaying rtPA treatment was documented but not the minutes lost. It is to be noted that in our stroke center CT scanner is sometimes down so the times measured above do not count.

Uncertainty about the symptom onset can be reduced by instructions and training for ambulance personnel. Government and medical professionals should educate the general population regarding stroke symptoms and improve cooperative EMS systems. Also, preparing an organized and comprehensive stroke program in the hospitals will improve acute stroke management in Iran. We suggest that other studies be conducted with a larger sample size in both urban and rural areas and future studies focus on prehospital and in-hospital delaying factors.

Conclusion

According to this study, although two-third of eligible patients were transferred to the hospital at the right time,

the rate of using EMS for patient transportation is low. More studies are needed to explore this phenomenon to enable health authorities in this issue.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of the Guilan University of Medical Sciences (IR.GUMS.REC.1395.302). All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki, 2013.

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Authors' contributions

Conceptualization: Mozaffar Hosseini-zhad and Seyyed Mahdi Zia Ziabari; Methodology: Rasoul Tabari-Khomeiran, Amirreza Ghayeghran, and Sedighe Esmailzadeh; Investigation: Mozaffar Hosseini-zhad, Yaser Moaddabi, and Sedighe Esmailzadeh; Writing the original draft, review, and editing: Mozaffar Hosseini-zhad, Rasoul Tabari-Khomeiran, Yaser Moaddabi, Amirreza Ghayeghran, Sedighe Esmailzade, Seyyed Mahdi Zia Ziabari, and Maryam Ghasemi; Resources: Rasoul Tabari-Khomeiran, Sedighe Esmailzade, and Maryam Ghasemi; Supervision: Mozaffar Hosseini-zhad, Seyyed Mahdi Zia Ziabari, and Amirreza Ghayeghran.

Conflict of interest

The authors declared no conflicts of interest.

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