Factors affecting pre-hospital and in-hospital delays at time-to-treatment and complications in stroke: A prospective cohort study

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Research Article

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Abstract

Background: Time-to-treatment affects the outcomes of acute ischemic stroke (AIS). The aim of this study was to determine the factors affecting pre-hospital and in-hospital delays in the time-to-treatment and complication in AIS.

Methods: This prospective study was performed on 204 AIS patients referred to the stroke care unit in Iran (Zanjan) in 2019. Data were completed by interviewing the patients, their families, records, and observations. The mortality and complication rates were recorded for 30 post-stroke days through call follow-up.

Results: The results showed that the highest delay was related to the onset-to-arrival time (288.19 ±339.02 minutes). Results of logistic regression showed that treatment delay declined significantly by consulting followed by symptoms onset, patient transfer through emergency medical service to the hospital, and patients' understanding of AIS symptoms. The results also showed that increasing the onset-to-treatment time (P< .001) and high National Institutes of Health Stroke Scale (NIHSS) score (P< .000) were the most important factors associated with post-stroke complications. High age (P< .044) and high NIHSS scores (P< .001) were significantly associated with mortality in patients with AIS.

Conclusion: Informing people about AIS symptoms and referring to AIS treatment units are essential in reducing the treatment time.

Background

Stroke is the most common neurological disease (1). Annually, 15 million people worldwide are affected by stroke, of which one-third die and one third suffer from a permanent disability (2). In Iran, acute ischemic stroke (AIS) occurs about 10 years earlier compared to the developed countries (3, 4). AIS is a medical emergency that critically needs treatment and care in the early hours such that its quick diagnosis and appropriate intervention can lead to favorable outcomes. On the other hand, with delayed treatment, it can result in significant complications, high mortality, and huge costs for the individual, the family, and the community health system (5, 6).

Recanalization and reestablishing blood flow to the brain tissue is the most effective strategy for the treatment of patients with AIS (7-9). Therefore, invasive and non-invasive therapies are used to achieve this goal. In the invasive and non-invasive procedures, mechanical devices (angioplasty), and recombinant tissue plasminogen activator (rTPA) are applied to reopen the blocked vessels (10, 11).

In 1996, the Food and Drug Administration (FDA) recommended the use of recombinant tissue plasminogen activator (rTPA) in patients with AIS during the first 3 hours of symptoms onset (12). American Stroke Association Standard (2018), in over 50% of patients eligible for rTPA, recommends brain imaging within less than 20 minutes, the interval of less than 60 minutes between the hospital arrival, and thrombolytic therapy (13). A fifteen percent reduction in patients' door-to-needle time (DTN) in

administering thrombolytic therapy is associated with a 4% improvement in clinical symptoms and a 5% reduction in mortality rate in AIS patients (14, 15).

A reason for not using rTPA is the waste of golden time of medication use due to delayed referring to hospital (16). Various factors, including pre-hospital and intra-hospital causes, may delay the time-to-treatment in AIS patients. Delays in identifying patients and delays in patient transfers are considered as the pre-hospital causes while delays in neurologic visits, delays in brain imaging, delays in decision-making in the treatment process are identified as intra-hospital delays cause in this regard (17, 18). In a study in Iran, 80.2% of patients did not receive rTPA due to a delay of over 4 hour and 30 minutes. The most important reason for the delay in these patients was the delay in referring to the hospital (19). In another study in Iran, the mean arrival time of the patients to the hospital and CT scan was 91 minutes, which is 66 minutes longer than the international guidelines, and the mean arrival time and receiving rTPA was 147 minutes, which is 87 minutes longer compared international guidelines (20). In a study in the USA, at least an effective delay factor was identified in 84.3% of patients, with the highest delay related to the imaging (21). In another study in Egypt, the mean onset-to-arrival time was 147.2 minutes and the mean time between the hospital arrival and rTPA injection was 87 minutes. The main causes of delay in patients were misperception of stroke symptoms and long distances from health centers (22).

Various factors, including the patient's delay after the onset of early symptoms and delay of treatment staff, are still accounted for a large proportion of the causes of non-timely treatment. Investigating the factors affecting the identification of pre-hospital and in-hospital delay factors in each community is important since it determines the quality of care delivery services and the individual factors influencing timely treatment. In Iran, in 2016, the stroke code or code 724 was notified by Iran's Ministry of Health to the medical universities for better treatment management of patients with stroke. Therefore, reviewing the status of pre-hospital and hospital delays in Iran is felt after implementing this plan in Stroke Care Units (SCU). Moreover, the best of our knowledge, there is no study in Iran to examine delays in pre-hospital and in-hospital simultaneously after implementation of code 724. Hence, the present study aimed to determine the factors affecting pre-hospital, in hospital, and time-to-treatment delays in acute stroke and their relationship with complications and mortality.

Methods

This descriptive cross-sectional study was conducted from July to the end of October at the SCU in Zanjan City (Iran) in 2019.

Study setting

Zanjan province is located in the northwestern part of Iran. The capital of this province is Zanjan city. This province has a population of 105,7461 people, 8 towns, and 978 villages. There are 10 hospitals affiliated with Zanjan University of Medical Sciences in the province. However, only Valiasr hospital in Zanjan University of Medical Sciences has a stroke care department and provides services for patients with ischemic stroke.

SCU in Zanjan opened at Vali-Asr Hospital in 2016 is known as the stroke treatment center in Zanjan Province. In Iran, code 724 is defined for stroke patients for whom less than 4 hour and 30 minutes have passed since the onset of stroke symptoms. According to the protocol code 724, as soon as the patient contacts Emergency Medical Services (EMS), the symptoms Face-Arms-Speech-Time (FAST) is asked from the patient. Then, after sending the ambulance to the patient's bedside, the FAST symptoms are checked by the emergency technician and after confirmation, the SCU is notified. If patients are in cities around the province, they are immediately transferred from all medical centers in the province to the SCU in that province. After transferring to the hospital, the patient is examined by a neurologist at the triage unit and sent to the CT scan unit if he/she is diagnosed with a stroke and the rTPA medication is administered there.

Sampling

In this study, patients with AIS were studied in the SCU of Zanjan. Sampling in this study was based on the convenience sampling. Patients referred to the SCU during the sampling interval with inclusion criteria were included in this study. Based on the pilot study on 20 AIS patients, the sample size of 181 was obtained with a sampling error of 20 minutes, effect size of .05 and a confidence level of 95%. In this study, 204 patients with AIS referring to the SCU were evaluated.

Data gathering

The data collection method in this study was observation and interviews with patients and, if necessary, with their families. The patients referred to the stroke ward at Valiasr Hospital in Zanjan entered the statistical community through direct observation and interviewing them or their companions. Then, a questionnaire related to demographic information and the time interval from the onset of initial symptoms to the beginning of therapeutic measures were completed. Since patients were monitored 24 hours a day during their hospital stay, this period was covered by two researchers. The patients were followed up in the neurology unit, Intensive care unit and SCU, as well as thirty days after discharge, by the researchers. The data collection tool was a researcher-made questionnaire that identified information on demographic characteristics and factors affecting the time-to-treatment and the average duration of onset of symptoms to treatment. The questionnaire was designed in three parts. The first part included questions about patients' demographic characteristics. The second part included questions about the reasons for pre-hospital delays. The third part of the questionnaire included questions about the reasons for in-hospital delays (Appendix No. 1). To check the frequency of complications, a list of common complications after acute strokes based on papers related to strokes was used. A total of 28 stroke complications were checked by the checklist for one month after the acute stroke (Appendix No. 2). Complications and mortality during patient hospitalization were recorded through observation and after discharge from the hospital by telephone contact with patients or their families. If the patient died after discharge, the patient's medical record would be examined to determine the stroke-related causes of death and its complications. These data were approved by the treating physician. The severity of AIS was also assessed using the National Institutes of Health Stroke Scale (NIHSS). This instrument contains 11

items. For each item, a score of 0 represents the average performance of the individual in the studied filed, and a score of 4 indicates the highest impairment in this regard. In this scale, the minimum and maximum scores are 0 and 42, respectively. Here, a score of 0 indicates no symptoms of stroke, 1 to 4 mild strokes, score 5 to 15 moderate stroke, 16 to 20 moderates to severe stroke, and 21 to 42 the severe stroke. In-hospital mortality rates were also assessed by observation and 30-day mortality rates through telephone calls with patients or their families.

Content validity was used to determine the validity of the questionnaire. The designed questionnaire was provided for 10 experts and the necessary modifications and changes were made based on their opinions. The reliability of evaluators was used to assess reliability. Two researchers completed the questionnaire simultaneously for 10 patients. Then, Cohen's kappa coefficient was evaluated between the data of the questionnaire completed by these researchers and the reliability of the evaluators was confirmed by obtaining K = 0.973. The validity and reliability of the NIHSS tool were confirmed by Kasner et al (23).

Ethical considerations

This study was performed with the approval of the Ethics Committee of Zanjan University of Medical Sciences and obtaining Ethics Code (IR.ZUMS.REC.1398.095). The researcher explained the inclusion criteria to the patients or their families who were eligible to participate in the study, and written consent was obtained if they desired. The participants were assured that all their information would be confidential and that they could be excluded at any time. Patients also had the right to withdraw from the research at any moment.

Procedures

In this study, the patients referring to the SCU with the inclusion criteria were selected. The 60-item questionnaire was completed by the researcher after relative stabilization and treatment by the aid of the patient or his/her caregivers. The checklist was used to assess and evaluate complications, which was completed within the first week to 4 weeks after acute stroke. The complications and mortality were assessed during the hospitalization and it was completed after discharge through telephone calls with patients or their families.

Variables

The variables of this study included demographic variables, stroke risk factors, effective factors related to pre-hospital and in-hospital times for initiating treatment, complications, and mortality. Also, the complications of stroke were considered based on the presence of at least one complication on the checklist. The mortality rate from stroke complications in the hospital, as well as 30 days after hospitalization, was assessed.

To find the mortality rate, all patients were followed up to 30 days after hospitalization. If mortality occurs within 30 days of hospitalization due to AIS, patients' medical records should be reviewed to determine

the cause of AIS mortality.

Data analysis

Statistical analysis was performed using SPSS V.16. The distribution of the data was based on sample size and normalized central limit theorem. Logistic regression was used to investigate factors associated with the delay in treatment and factors associated with complications and mortality. The significance level of less than .05 was considered in this study.

Results

In this study, 230 patients with stroke were referred to the SCU from the first of July to the end of October 2019. Data from 10 patients with hemorrhagic stroke and 16 patients with the transient ischemic attack were excluded from the study. Finally, the data of 204 patients with acute ischemic stroke referred to the SCU were examined. The diagnosis of ischemic stroke in these patients was determined by the treating physician.

A total of 204 patients participated in this study, of which 55.9% were male, 72.5% were illiterate, and 19.6% had a high school diploma. The mean age of participants was 68.99 ±13.91 years. Among the patients, 50% lived in Zanjan. According to the patients' statement, 54.4% had insufficient income and 87.7% had at least one risk factor. The most common risk factor for AIS was hypertension (59.3%), with ischemic heart disease placing in the second rank (30.4%). Also, about 77.9% of the patients were at home at the onset of symptoms.

In 52% of the patients, the stroke severity was moderate. The mean hospitalization period was 6.48 ± 5.64 days. In this study, 140 (68.6%) patients with code 724 were referred to the SCU and they arrived at the hospital within the interval of less than 4 hour and 30 minutes after the onset of the symptoms. About 129 (63.2%) patients received rTPA, while 75 (36.8%) patients did not receive it. The reason for not receiving rTPA in 64 (31.4%) patients was the delay of more than 4 hour and 30 minutes from the onset of symptoms to referral to SCU. At the end of the first month, 31 (15.2%) patients died and 38 (18.6%) patients had at least one complication.

In this study, 70.6% of the patients considered their primary symptoms as other disease symptoms and did not believe that they had a stroke. Also, 17.2% of them did not consult anyone after the onset of symptoms and did not take any action. About 47.5% of the patients referred to medical centers rather than SCU after the onset of symptoms, with the majority (30.4%) referring due to proximity or availability. Moreover, 46.1% of them referred to SCU by personal vehicle. For more than half of the patients (62.7%), the first visit was performed by a neurologist (Table 1).

In the present study, the mean onset-to-arrival time was 288.19 ± 339.02 minutes and the mean onset-to-treatment time was 314.13 ± 341.04 minutes, among the pre-hospital delay factors, the delay when deciding to contact the Emergency Department or the attempt to refer to medical centers (204.74 ±

321.38 minutes) was longer than the time of patient transfer to the hospital (83.52 ±72.38 minutes) (Table 2).

In this study, logistic regression was used to investigate the predictors of the onset-to-treatment time. In logistic regression, the presence or absence of delay in arriving at the hospital was considered as the dependent variable, the patients who referred SCU within 4 hour and 30 minutes were regarded without delay and the patients referring SCU after this time were considered as with delay. The results of logistic regression showed that consulting with a person after the onset of the symptoms, referring to the Emergency Department and proper understanding of the patients regarding stroke symptoms were identified as the strongest predictors of reduced delay until treatment onset (Table 3). The logistic regression results indicated that increasing the onset-to-treatment time and high NIHSS scores were the most important predictors of complications (Table 4). Moreover, higher age and NIHSS scores were the most significant predictors of mortality in patients after stroke (Table 5).

Discussion

The results of this study showed that pre-hospital delay was longer than hospital delay. Among the pre-hospital factors, the delays in the decision to call the Emergency Department or attempt to refer to the medical treatment were longer than the time of patient transfer to the hospital.

In the study of Ghiasian et al in Hamadan, Iran, the time of symptoms initiation to arrival to the hospital was 282 minutes and it was 192 minutes in the study of Griesser et al (24, 25), which is close to our results. However, it was 916 minutes in the study of Ayromlou et al, in Tabriz, Iran, which is inconsistent with our study (20). This study was conducted in the Tabriz metropolitan area and delay in the arrival of patients could be due to traffic problems in this city. Equipping smaller towns around the provinces with SCUs, the presence of neurologists, accurate diagnosis of the stroke, and administering thrombolytic medication can dramatically reduce the onset-to-treatment time.

In Ruiz's et al study in Spain, the mean onset-to-arrival time was 201 minutes and the mean onset-to-decision time was 72 minutes (26). Moreover, in Faiz's study in Norway, these times were 179 minutes and 92 minutes, respectively (27). Contrary to the results of our study, there was less delay in decision making in these two studies.

Investigating transfer with EMS in all studies of Ruiz et al, Koksal et al, Faiz et al, Springer et al, Sobral et al, and Haiqiang et al reduced the delay in arrival to hospital (26-31). In our study, patients referring to EMS also experienced less delay. In the present study, most patients referred initially to other treatment centers because of the proximity or availability or referred to SCUs late due to ignoring the initial symptoms. Examination of stroke symptoms by EMS technicians might be an effective step toward faster transfer of these patients to the hospital

In line with our study, the results of studies performed in Europe, America, and Asia indicated that lack of awareness of stroke symptoms, patients' misconceptions and beliefs regarding the primary symptoms,

and failure to consult a person after the onset of the symptoms led to further delay in arrival to the hospital and time-to-treatment for stroke patients (22, 24, 26-29, 31-33). The findings suggest that consulting with others following the onset of symptoms may be effective in preventing a delay in cases the patient's symptoms are not well recognized or taken seriously.

The results of our study investigating the hospital delay factors in AIS patients indicated that there was no delay in AIS patients receiving code 724. In this study, the interval between hospital arrival to brain CT scan (10.60 ± 6.79 minutes) and between hospital arrival interval to rTPA implementation (25.18 ±17.01 minutes) was much less than the time suggested by the American Stroke Association guidelines (13). In Huang's et al study in China, the mean time to first visit in code 724 patients was 10 minutes, the mean CT scan time was 28 minutes, and the mean rTPA injection time was 116 minutes (34). In the study of Hsiao et al, the mean time to first visit was 6 ± 2 minutes, the mean time of arrival to brain imaging was 11 ± 7 minutes, and mean patient arrival time to thrombolytic injection was 63 ± 23 minutes (35). In the study of Ayromlou et al in Tabriz, Iran, the mean time of patients' arrival to the hospital and CT scan was 91 minutes, which was 66 minutes longer than the international guidelines, and the mean time of patients' arrival to the hospital and receiving rTPA was 147 minutes, 87 minutes longer compared to the international guidelines (20). In the Dhaliwal et al study in the United States, the mean initial CT scan time was 13.66 minutes, the CT scan interpretation time was 25.20 minutes, and the time between the patient's arrival and rTPA injection was 51.27 minutes (36). In the study of Hasankhani et al in Tabriz, Iran, the meantime between hospital arrival and rTPA injection was 69 minutes (19). In Mowla's et al in New York, the highest imaging delay was over 25 minutes (21). In the results obtained from studies in Iran and foreign countries, the time between hospital arrival and time-to-treatment in patients with code 724 is much longer compared to the results of the present study. This finding suggests that the management of the stroke code team in stroke patients at SCUs could have a significant impact on reducing the time-to-treatment in these patients. In the present study, among the factors related to one-month complications in patients, the AIS severity of and the onset-to-treatment time was the best predictor for complications in stroke patients. Moreover, the severity of the AIS and high age were the most important predictors of mortality in patients with AIS. In the study of Denti et al in Italy, mortality risk was significantly lower among stroke patients referring to the hospital earlier, and there was a significant correlation between pre-hospital delay and severity of neurological score with mortality rate. In this study, patients with a stroke severity of less than 18 had a better outcome (37). In our study, the high neurological score was also significantly associated with mortality. Consistent with our study, in the study of Jung et al in Georgia, patients receiving rTPA in less than 45 minutes had a better outcome within 90 days (38). In the Faisal et al study in Qatar, by reducing the DTN time between 2008 and 2015, the complication rate decreased from 15.7% to 8.8% (39). In line with the results of our study, in the study of Oliveira et al in Brazil, there was a significant correlation between older age and the mortality rate in patients with stroke (40).

Conclusion

According to the results of this study, the pre-hospital delay was longer than hospital delay in case of stroke events. Among the pre-hospital delay factors, the delay when deciding to call the EMS or finding a medical center was longer compared to the time of transferring the patient to the hospital. In other words, a large portion of the delay causes in pre-hospital factors is due to the delay in patients' decision to refer to the hospital. It seems that informing at-risk people, especially those over 60 years, regarding the stroke risk factors, the early symptoms of stroke, and the importance of rapidly initiating treatment to improve the outcomes of the disease, will help patients understand their symptoms properly so that they can be delivered to the hospital faster by contacting the emergency system.

Limitations

One of the limitations of this study was the low accuracy of reminding the times, especially by elderly patients. The researchers attempted to accurately record the times and factors affecting pre-hospital delays by emphasizing important times such as Azan time, news time, and events of the day. Considering the cultural and geographical location of Zanjan, the results of this study are not generalizable to other communities.

Abbreviations

NIHSS, National Institutes of Health Stroke Scale; FDA, Food and Drug Administration; rTPA, recombinant Tissue Plasminogen Activator; DTN, Door-To-Needle time; SCU, Stroke Care Unit; AIS, Acute Ischemic Stroke; CT scan, A computed tomography scan.

Declarations

Ethics approval and consent to participate

This research was conducted after granting the approval of the ethics committee of Zanjan University of Medical Sciences and obtaining an ethical code (IR.ZUMS.REC.1396.305). All methods were carried out in accordance with relevant **guidelines and regulations.** Ethics approval and consent to participate Institutional review board approved and all participates consented. Written informed consent was obtained from all participants.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NH designed the study, carried out statistical analyses of the data, was involved in the interpretation of the data and wrote the manuscript, NG collected the data, was involved in the interpretation of the data, MR D was involved in the interpretation of the data. All authors read and approved the final manuscript.

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Tables

Table 1. The frequency of participants based on patients’ perception of symptoms and their way of referral to medical centers

N (%)	**Variables**	
60 (29.4)	Neurology	Patient perceptions of early symptoms
144 (70.6)	Non-neurology	
49 (24)	Spouse	Consultation after the onset of symptoms
94 (46.1)	Children	
4 (2)	Colleague	
18 (8.8)	Relatives	
4 (2)	Nurse	
35 (17.2)	Not consulting anyone	
107 (52.5)	Referral to SCU in Zanjan	Patient referral after symptom onset
55 (27)	Other medical centers	
28 (13.7)	Clinic	
13 (6.4)	Private office	
1 (0.5)	Private hospital	
62 (30.4)	Proximity or availability of the center	Reasons for referral to a treatment center other than SCU
8 (3.9)	Not awareness of stroke center at SCU	
27 (13.2)	Not considering the disease seriously by the patient	
94 (46.1)	By personal vehicle	Referral
64 (31.4)	By Emergency Services (EMS)	
44 (21.6)	Referral by ambulance from other medical centers	
1 (0.5)	Stroke inside the hospital	
1 (0.5)	Air Emergency	
2 (1)	General Practitioner	The first visitor of the patient
128	Resident of Neurology	

(62.7)	
68 (33.3)	Emergency medicine specialist
5 (2.5)	Neurologists
1 (0.5)	Non-neurology Resident

Table 2. The mean of the time interval between onset of symptoms and treatment based on pre-hospital and in-hospital factors

Mean ± St. Deviation(min)	Confidence interval (min)	Variables	
204.74±321.38	160.38-249.10	Onset –to- decision time	**Pre-hospital time intervals**
83.52±72.38	73.53-93.52	The transfer time	
288.19±339.02	241.39-334.99	Onset –to- arrival time	
3.07±2.46	2.66-3.49	Door –to- examination time (code stroke)	**In-hospital time intervals**
10.6±6.87	9.39-11.82	Door –to –imaging time (code stroke)	
17.99±13.13	15.77-20.21	Door –to –SCU entry time (code stroke)	
21.87±13.94	19.57-24.18	Door –to- treatment decision making (code stroke)	
23.08±16.46	20.22-25.93	Door-to- order time (code stroke)	
25.01±16.97	22.05-27.96	Door –to- Needle time (code stroke)	
15.08±8.51	12.94-17.22	Door –to- examination time (No code stroke)	
214.98±193.49	166.65-263.32	Door –to –SCU entry time (No code stroke)	
29.07±33.82	20.33-37.80	Door –to –treatment time (No code stroke)	
314.13±341.04	267.05-361.21	Onset –to – treatment time in stroke patients	

Table 3. The predictors of symptom initiation to arrival to SCU

95% C.I.for EXP(B)		Logistic regression analysis						variables
Upper	Lower	EXP(B)	Sig.	df	Wald	S. E	B	
1.047	.929	.986	.646	1	.211	.031	-.014	Stroke Intensity (NIHSS)
.518	.036	.136	.003*	1	8.575	.680	-1.992	Patient perceptions of early symptoms
800.241	20.598	128.386	.000*	1	27.042	.934	4.855	Consultation after the onset of symptoms
31.155	2.250	8.372	.002*	1	10.045	.670	2.125	Transportation by Emergency medical service
3.194	.597	1.381	.451	1	.569	.428	.323	Sex
1.063	.988	1.025	.193	1	1.696	.019	.025	Age
5.734	.593	1.845	.290	1	1.120	.579	.612	Risk factor
		.010	.002	1	9.478	1.504	-4.631	Constant

*P-value< .05

Table 4. The predictors of stroke complications during one month after stroke

95% C.I.for EXP(B)		Logistic regression analysis						variables
Upper	Lower	EXP(B)	Sig.	df	Wald	S. E	B	
1.229	1.074	1.149	.001*	1	16.163	.035	.139	Stroke Intensity (NIHSS)
1.003	1.001	1.002	.001*	1	11.974	.001	.002	Symptom Onset-to-treatment time
		.036	.001	1	37.911	.541	-3.333	Constant

*P-value< .05

Table 5. Predictors of mortality one month after the stroke

95% C.I.for EXP(B)		**Logistic regression analysis**						Variables
Upper	Lower	EXP(B)	Sig.	df	Wald	S.E	B	
7.652	2.560	4.426	.001*	1	28.347	.279	1.487	Stroke Severity (NIHSS)
1.002	.999	1.001	.482	1	.495	.001	.001	Onset-to- treatment time
1.082	1.001	1.041	.044*	1	4.063	.020	.040	Age
		.000	.000	1	27.407	1.637	-8.568	Constant

*P-value< .05