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Research Article

Time Barriers to receiving recombinant tissue plasminogen activator in patients with acute ischemic stroke

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Abstract:

Objective: This study aimed to evaluate the barriers and limitations of receiving recombinant tissue plasminogen activator (rtPA) in patients with acute ischemic stroke.

Methods: The present study is a cross-sectional study that was performed on 188 patients with ischemic stroke who were referred for rtPA treatment. Patient records were quarried for demographic information and timelines of events from onset of symptoms and Emergency Department referral to rtPA treatment invitation. Patients were divided into groups of rtPA receiving group and the non-rtPA group. Collected data were analyzed by SPSS 20 software.

Results: The mean age of patients was 67.28±12.55 years. Meantime to emergency physician visit (P=0.2), the average time to neurologist visit (P = 0.3), the average time to CT scan (P=0.08), and average time to CT scan interpretation (P = 0.4) had no statistically significant difference between the rtPA receiving group and the non- rtPA group. But the average time from the onset of symptoms to reaching the emergency room (P = 0.001), the average time until the patient was assigned to a neurologist (P = 0.05), the average time from the emergency physician visit to the first instruction by the nurse (P = 0.02), the average time to blood test preparation (P = 0.001) and mean NIHSS score (P = 0.005) in the rtPA group were significantly lower than the non-rtPA group.

Conclusion: According to the findings, delay in referring patients to medical centers is the most important obstacle to not receiving rtPA. There are also several inhibitory factors from the time of entering the emergency room to receiving rtPA, but all of these factors can be intervened based on further researches.

Keywords: Acute ischemic stroke, tissue plasminogen activator, rtPA, timeline.

Introduction

Stroke, as a vascular disease of the brain, plays a very important role in the disability and mortality of adults, bringing socio-economic burden and rehabilitation problems. Clinically, stroke presents with a variety of symptoms including changes in the level of consciousness, physical, motor, cognitive, perceptual disorders, language function disorders, and pain *(1)*. Stroke is the most debilitating neurological disease and is the third leading cause of death in developed countries, accounting for 22

million deaths worldwide each year. About 75,000 people in the United States experience stroke each year *(2)*. In China, 1,500,000 people die each year from stroke *(3)*. Twelve percent of deaths in the UK are due to stroke. About 7% of hospital beds in Scotland are occupied by stroke patients *(4)*. According to epidemiological data, about 2 to 4% of the world's health care costs are allocated to stroke. Treatment of acute stroke is one of the most important challenges of medical health problems *(5)*. In general, there are two treatment strategies for this disease, which include cerebral reperfusion and neuroprotection *(6, 7)*. During the last decade, significant advances have been made in the development of thromboembolic therapies for the treatment of acute ischemic stroke, the most effective of which is the prescription of a recombinant tissue plasminogen activator (rtPA) in the first 4.5 hours after the onset of acute symptoms. Three months after rtPA injection the clinical complications of stroke get decreased significantly *(8)*. Tissue plasminogen activator is a protease serine with the corresponding gene on human chromosome 8 (12P8) that catalyzes the conversion of plasminogen to plasmin. This property is due to its ability to break down fibrin-containing clots, such as those in thrombotic brain lesions *(9)*. In order to use this treatment, conditions are needed that are not available in all centers, and providing them requires the full cooperation of patients, medical staff, and the provision of facilities in medical centers *(9-11)*. The most inhibitory factor in rtPA injection is the delay in diagnostic and therapeutic measures (such as a delay due to doctor's visit to the hospital and delay in preparing computerized tomography (CT) scan results and tests, etc.) as well as patients' delay in referring to the hospital; This study was designed to investigate the effect of timelines of symptom onset to rtPA injection on the success of receiving rtPA in patients with acute ischemic stroke.

Methods

This is a cross-sectional study that was performed on patients with ischemic stroke in 2019 who were in the rtPA treatment window (the interval between the onset of sudden stroke symptoms and the patient reaching the front door of the emergency room) and agreed to participate in the study. Study sampling was available simple sampling from all stroke patients in Ghaem Hospital in Mashhad. patients who were referred outside the treatment window, patients with hemorrhagic stroke, and patients who did not consent to rtPA treatment were excluded from the study.

Patients with ischemic stroke were eligible for intravenous rtPA based on the following conditions, which included all clinical and laboratory factors showing indications of rtPA treatment. indications of receiving rtPA include symptom initiation of fewer than 4.5 hours, no gastrointestinal or urinary bleeding in the last 21 days, no major surgery in the last 14 days, no head trauma, no stroke or myocardial infarction in the last two months, no active bleeding and evidence of acute trauma, no history of intracerebral hemorrhage, no oral anticoagulants, no symptoms of subarachnoid hemorrhage, no seizures at the onset of stroke, no post-ictal symptoms, diastolic blood pressure less than 110, systolic blood pressure less than 185, international normalized ratio (INR) less than 1.7, no heparin use in 48 hours before, platelet count more than 100,000, partial thromboplastin time (PTT) less than 50, no Evidence of intracerebral hemorrhage, serum glucose greater than 50 and less than 400, National Institutes of Health Stroke Scale (NIHSS) not less than 4 and not more than 25 *(11)*.

Study outcomes:

For patients eligible to receive rtPA, the interval between the onset of acute stroke symptoms and the patient's arrival In the emergency room (Symptom To Door), the interval between the emergency physician visit and the nurse's execution of the first order, the neurologist visit interval from the patient

referral, Door-to-Puncture Time (DTPt), door to imaging time (DTIt), time interval receiving rtPA from time to door to needle time (DTNT), NIHSS score, and the interval between preparation of laboratory results were recorded.

Data collection checklists were completed by the manager resident. Finally, the collected information was entered into SPSS (Statistical Package for the Social Sciences) version 20 software and then submitted to a statistician for analysis. Mann-Whitney test was used to analyze the data due to abnormal data distribution. Statistically, a significant level was considered at a p-value <0.05.

Results

In this study, 188 patients were included in the study, of which 112 (59.6%) were males and 76 (40.4%) were females. The mean age of patients was 67.28±12.55 years. One hundred forty-eight patients (78.7%) were transported to the hospital by emergency medical service (EMS) and 40 patients (21.3%) were self-referred to the hospital. Mean systolic blood pressure was 153.75±26.82 (mm Hg), mean diastolic blood pressure was 14.52 ± 90.31 (mm Hg), mean heart rate was 10.64 ± 82.70 (bpm), mean respiratory rate was 16.38±2.16, mean initial glycemic index was 158.87±80.58 (mg/dl) and mean SPO2 in patients was 95.98±2.53. The level of triage was level 2 in 165 patients (87.8%) and level 3 in 23 patients (12.2%). The initial complaint in 83 patients (24.7%) was of right hemiparesis, left hemiparesis in 97 patients (28.9%), in 108 patients (32.2%), speech disorder in 42 patients (12.5%), and altered level of consciousness in 6 patients (1.8%). In the study of past disease history, 71 (21.4%) had a history of Diabetes Mellitus, 132 (39.8%) had a history of hypertension, 78 (23.5%) had a history of heart disease, 31 (9.3%) had a history of cerebrovascular accident, 1 (0.3%) had a history of epilepsy, 2 (0.6%) had a history of atrial fibrillation, and 2 (0.6%) had a history of chronic kidney disease. In addition, 15 patients (4.5%) had no history of any disease.

Meantime from the onset of symptoms to arrival at the emergency room was 75.19 ± 94.82 minutes (about an hour and a half), the average time to visit the emergency physician was 8.85 ± 8.81 minutes, the average time to visit the neurologist was 2.25 ± 17.80 minutes; the average time to perform a CT scan 10.61 ± 19.95 minutes, mean time to CT scan interpretation was 21.22 ± 30.11 minutes; meantime to patient assignment to the neurologist 48.48 ± 69.71 minutes (more than one hour); the mean distance from emergency physician visit to first order by the nurse was 6.42 ± 15.65 minutes; the mean time between triage to receive rtPA was 33.29 ± 88.76 minutes (about one and a half hours); the meantime from the onset of symptoms to receiving rtPA 56.86 ± 164.11 minutes (about 2 hours and 45 minutes); the mean time interval between preparation of the blood tests results was 12.36 ± 37.86 minutes, and the mean NIHSS score was 12.77±2.77.

The results of reviewing and comparing the timelines between patients who successfully received rtPA and those who didn't receive it are shown in Table 1. When assessed according to the meantime to emergency physician visit (P = 0.2), the average time to neurologist visit (P = 0.3), the average time to CT scan preformation (P = 0.08), and average time to CT scan interpretation (P = 0.4), there was no statistically significant difference between the rtPA receiving group and the non- rtPA group.

But for the average time from the onset of symptoms to reaching the emergency room (P = 0.001), the average time until the patient was assigned to a neurologist (P = 0.05), the average time from the emergency physician visit to the first instruction by the nurse (P = 0.02), the average time of blood tests' results preparation time (P=0.001), and mean NIHSS score (P = 0.005) there were significantly lower values in the rtPA group than the non-rtPA group.

Table 1. timelines of receiving rtPA in rtPA and non- rtPA patients

		Mean	SD	P-value
The time of onset of symptoms until reaching the emergency room, min	rtPA	78.02	42.73	0.001
	non- rtPA	125.03	106.18	
Time to visit an emergency physician, min	rtPA	8.84	8.23	0.2
	non- rtPA	8.76	0.90	
Time to visit a neurologist, min	rtPA	16.99	16.54	0,3
	non- rtPA	19.23	5.57	
Time to do a CT scan, min	rtPA	20.57	9.90	0.08
	non- rtPA	18.77	11.84	
Time to interpret CT scan, min	rtPA	29.20	13.87	0.4
	non- rtPA	31.85	30.78	
Time until the patient is assigned by a neurologist, min	rtPA	62.31	31.15	0.05
	non- rtPA	84.01	69.02	
visit of the emergency physician to the execution of the first order by the nurse, min	rtPA	12.55	5.39	0.02
	non- rtPA	17.48	20.11	
Interval preparation time for tests, min	rtPA	35.03	9.95	0.001
	non- rtPA	55.55	11.57	
NIHSS score	rtPA	7.39	4.76	0.005
	non- rtPA	13.64	23.56	

In the end, rtPA was prescribed for 119 patients (63.3%), which after receiving it, showed relative improvement in 111 patients (93.3%) and the outcome was appropriate in two patients (1.7%), but the condition of three patients (2.5%) did not improve after rtPA administration (two patients (1.7%) lost consciousness and one (0.8%) suffered brain death).

Examination of complications of rtPA administration in patients revealed that 11 patients (9.2%) died, 14 patients (11.8%) had Intracerebral hemorrhage (ICH), two patients (1.7%) had Gastrointestinal Bleeding (GIB), and one patient (0.8%) had Intraventricular hemorrhage (IVH).

rtPA was administered in 34 patients (28.6%) in the neurosurgery ward, 79 patients (66.4%) in CCU, and 6 patients (5%) in ICU.

Discussion:

The results of our study showed a higher prevalence of stroke among men (59.6%). These results are consistent with the results of studies conducted in Europe *(12)* and the United States *(13)* and Arab countries *(14)*, which confirm that the risk of this disease is higher among men. In recent studies on the differences between men and women, the overall incidence of stroke was 33% higher in men than in women. Except for a few studies that had small sample sizes and poor results *(15)*. In Europe, the annual incidence of stroke was 1.0 to 2.9 per 1000 people in men and 0.6 to 1.9 per 1000 people in women *(16)*. The proportion of strokes with epidemiological changes and population aging is likely to increase *(17)*. In our study, the mean age of patients was 67.28±12.55 years, which indicates that age is one of the most important risk factors for stroke.

According to the results of our study, the average time from the onset of symptoms to reaching the emergency room was 75.19 ± 94.82 minutes (about an hour and a half). It seems that the lack of knowledge about the symptoms of stroke in our society might be the main reason for this delay in referring to medical centers. Katzan et al. Also noted that 15% of patients with an ischemic stroke presented within three hours, and the most common

reasons for this were mild neurological deficits and rapid improvement in symptoms *(18)*. It can be said that the more obvious and dangerous the symptoms of the disease contribute to a faster referral to the hospital. In general, it can be concluded that the delay in referring patients with stroke to medical centers is due to two cultural problems and a lack of knowledge about the importance of the issue or the long-distance to refer to medical centers.

In our study, only 63.3% of potential rtPA candidates received the medicine. Ideally, more than 40% of all stroke patients should receive rtPA *(19)*. In the study of Hatamabadi et al., 171 patients with stroke were studied. Reasons for not injecting medicine in 104 people (70.3%) was Loss of golden time, in 31 cases (20.9%) was the existence of drug prohibition, in 8 cases (5.4%) were lack of intensive care bed and in 5 cases (3.4%) the reason was financial inability to afford it. The mean time between the patient's arrival in the emergency room and the doctor's visit, CT scan, neurological consultation, and the final decision for the patient was 11, 112, 211, and 320 minutes, respectively *(20)*. According to the results of our study, the average time to visit an emergency physician was 8.85 ± 8.81 minutes, the average time to visit a neurologist was 2.25 ± 17.80 minutes, the average time for CT scan was 10.61 ± 19.95 minutes, the average time to interpret C T-scan was 21.22 ± 30.11 minutes. Compared with Hatamabadi et al. study, our study shows a much better average time from the patient's arrival in the emergency room to the final decision, and this is one of the reasons for the contradiction between the results of our study and Hatamabadi's study in the administration of rtPA.

Based on our results, it can be said that the delay in visiting patients with stroke by an emergency physician is one of the important reasons for preventing medication. In our study, fortunately, the average time was 8.85 ± 8.81 minutes, which indicates the good performance of emergency physicians in Ghaem Hospital.

The mean NIHSS score in our study was 12.63±2.77. Also, the mean NIHSS score in the rtPA group was significantly lower than in the non-RTPA group. In the study of Saver et al., The NIHSS criteria recorded before treatment in 87.7% of patients was 11 *(21)*. In the study by Grotta et al., 15% of all patients with acute cerebral ischemia were having a mean NIHSS of 14±6 and the NIHSS rate in patients with in-hospital mortality (15%) was 7.7% *(22)*.

Due to the importance of time in dealing with patients with acute ischemic stroke, these patients should be given priority by the emergency physician after visiting the emergency room. In this regard, we can refer to the study of Sushma et al. In 2015, which finally concluded that the reason for the delay in receiving thrombolysis is the lack of a stroke education program for most people and the lack of priority for stroke patients in triage *(23)*. Other hospital factors such as the average time to the emergency physician visit, neurologist visit, CT scan, CT scan interpretation, the distance of the emergency physician visit to the first instruction by the nurse, and the interval between the preparation of tests in our study compared to standard recommendations was acceptable; and only the neurologist's assignment of the patient (more than one hour) could be one of the barriers to receiving tissue plasminogen activator. In this regard, Kobayashi et al. recommend the use of a second-line physician who only cares for patients with acute stroke *(24)*. Sushma et al. (2018) also stated that the implementation of the Stroke Code scheme helps us to increase thrombolysis interventions in patients with acute ischemic stroke and reduce the time to receive tissue plasminogen activator *(25)*.

Conclusion:

According to the findings of our study, the most significant barrier to getting a tissue plasminogen

activator is the delay in referring patients to medical institutions. From the moment you reach the emergency department to the time you get the tissue plasminogen activator, there are numerous inhibiting variables to consider, but all of them may be managed easily. Therefore, it is recommended that sufficient information be provided about the disease and its symptoms and that its common symptoms be educated through the public media and physicians.

Ethics approval and consent to participate:

The study was approved by the Institutional Review Board of Mashhad University of Medical Sciences.

Consent For Publication:

Not Applicable.

Availability of Data and Materials:

All data are available in the article.

Competing interests:

None.

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Authors' contributions:

MF and RG designed the study. EP and RG quarried patient records for assessing timelines. The manuscript was written by EP and RG and revised by MF.

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