Investigating the Effect and Immunity of Tissue Plasminogen Activator in the Treatment of Acute Ischemic Stroke

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Abstract: *Background and Objective*: Although current evidence has demonstrated the efficacy and immunity of Alteplase, further studies are needed to evaluate its functioning in the therapeutic system. This study aims to assess the effect and immunity of tissue plasminogen activator (tPA) in the treatment of acute ischemic stroke (AIS).

Methods: This study was conducted as a retrospective observational study on patients with AIS referred to Ahvaz Golestan Hospital in 2017-2018. By using the hospital database, demographic information, the cause of lack of thrombolytic therapy, the onset of symptoms and admission were extracted. The National Institutes of Health Stroke Scale (NIHSS) at the time of referral, 24 hours after treatment, and at the time of discharge, the modified Rankin Scale (mRS) scores at discharge time and 3 months after discharge, complications and mortality at the time of admission and 3 months after discharge were recorded.

Results: The mean of the event to needle (hrs) was significantly lower in the tPA group ($P < 0.0001$), and delay in visiting time and loss of golden time were of the main reasons for not receiving tPA in the control group. The mean difference and the decrease in NIHSS score 24 hours after admission and discharge in the tPA group was significantly higher ($P < 0.0001$). At the time of discharge, the mean score of mRS in the two groups was not significantly different. Three months after treatment, the mean score of mRS in the tPA group was significantly lower than that in the control group ($P < 0.05$). The percentage of patients with bleeding complications was higher in the tPA group (7.27%) than that in the control group (4.89%). The percentage of deaths during the hospital stay in the tPA group (3.64%) was higher than that in the control group (1.63%).

Conclusion: Patients with AIS under intravenous thrombolytic therapy with tPA showed improvement in functional measurements and neurological outcomes compared with the control group. Lack of significant difference in the rate of complications and mortality between the two groups indicated the safety and high efficacy of thrombolytic therapy in patients with AIS.

Keywords: Acute ischemic stroke, Thrombolytic therapy, NIHSS, mRS.

INTRODUCTION

Acute ischemic stroke (AIS) is a common disorder and a medical emergency that is reported annually by more than 700,000 new cases, or recurrence, in the United States [1]. The incidence and outbreak of AIS vary in different regions and races and its risk increases by ageing [2-5]. The brain injury process caused by AIS is complicated due to different cellular outcomes due to incomplete or complete ischemia [6]. The changes that occur during the onset of AIS vary from person to person and depend on factors such as temperature, metabolic factors such as blood glucose and peripheral blood supply to the related areas [7, 8]. Thus, interventions that can return cerebral blood flow to ischemic areas as quickly as possible and establish peripheral blood flow, as well as drugs that affect the ischemic cascade, can affect AIS. In recent years, the emergence of thrombolytic drugs has opened new horizons in the treatment of this disease. Intravenous thrombolysis is currently approved for AIS patients [9], and its safety and efficacy has proven in numerous studies [10-12]. Currently, the most appropriate treatment for AIS is the use of tissue plasminogen activator (tPA) in the form of intravenous or arterial, which is a serine protease and catalyzes the conversion of plasminogen to plasmin. As a result, it is able to break down fibrin-containing clots, such as clots in the vascular thrombotic lesions [13]. However, the use of tPA also has its own limitations, such as short life span (4-8 minutes), effects on the blood-brain barrier and neurotoxicity, the risk of intracerebral haemorrhage, and a long list of contraindications [1]. In developed countries, more than 10% of patients (up to 31%) are receiving thrombolytic therapy for AIS [14, 15], while in developing countries, where the risk of death from non-communicable diseases such as cardiovascular and cerebrovascular events is more than 30% compared to developed countries (16), only 1-6% of patients treated with thrombolytic therapy mostly in cities [17-21]. Considering that Alteplase is the only standard treatment for acute ischemic stroke (sometimes with thrombectomy) and its efficacy and safety has been proven in major studies in the world [22-31], further studies are needed to evaluate the functioning of the treatment system. Therefore, the present study was designed to evaluate the effect and immunity of tissue plasminogen in the treatment of

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acute ischemic stroke in patients referred to the emergency department.

METHOD

After obtaining permission from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code of Ethics: IR.AJUMS.REC.1397.585), this study was conducted as a retrospective observational study on patients with acute ischemic stroke (AIS) referred to Ahvaz Golestan Hospital from September 2017 to September 2018. In this hospital, thrombolytic therapy with tPA in patients with AIS is performed according to the standard protocol.

By using a hospital database, all patients with symptom and final diagnosis of AIS were selected according to the time of referral, and patients with evidence of hemorrhagic stroke in Computed Tomography (CT) scan were excluded from the study. Patient information including demographic characteristics (age, gender), weight, risk factors for stroke (including hypertension, diabetes, hyperlipidemia, cigarette smoking, alcohol or drugs, ischemic cardiovascular disease, history of stroke), blood pressure and blood glucose at referral, CT-scan result, cause of thrombolytic treatment failure, symptom onset time, emergency notification time, hospital arrival time and initiation of treatment, The National Institutes of Health Stroke Scale (NIHSS) at onset, 24 hours after treatment and discharge, modified Rankin Scale (mRS) at the time of discharge, were extracted and recorded. Complications, including symptomatic or asymptomatic intracerebral haemorrhage, bleeding in other organs, and mortality were recorded. Additionally, 3 months after the admission, the patient or one of his relatives was contacted by phone and mRS score was evaluated. Also, patient records and mRS in three months after the receipt of the tPA drug were recorded in the safe implementation of treatment in stroke (SITS) system, which was used to obtain patient information. In case of death, it was also recorded during the mentioned period. In the group treated with thrombolytic, the injection of tPA drug was performed according to its standard protocol. Patients also received this medication in the absence of contraindications for prescribing tPA and reaching the hospital during the golden time. All data were analyzed and compared by statistical package SPSS) WINDOWS, version 22). For all statistical analyses, the significance level was set at 0.05.

RESULTS

In this study, 239 eligible patients were evaluated and compared in two groups, including tPA group (n= 55) and the control group (no tPA administration) (n= 184). There was no significant difference between

Table 1: Demographic Data of Patients in the Two Groups

	Variables	tPA (n=55)	Control (n=184)	P-value
Gender (N, %)	Female	26 (47.27%)	86 (46.49%)	0.82
	Male	29 (52.73%)	98 (52.97%)	
Age (year) (Mean ± SD)		66.62±11.96	65.14±14.93	0.503
Weight (kg) (Mean ± SD)		77.98±10.63	77.02±12.28	0.601
Underlying Diseases (N, %)	Hypertension	32 (58.18%)	111 (60.33%)	0.088
	Diabetes	17 (30.91%)	62 (33.69%)	
	Hypercholesterolemic	10 (18.18%)	39 (21.19%)	
	Cardiovascular	14 (25.45%)	44 (23.91%)	
	With history of Stroke	7 (12.73%)	29 (15.76%)	
	Smoking (N, %)	5 (9.09%)	16 (8.69%)	0.92
Blood Pressure (mmHg)	Systolic	154.51±29.62	157.79±30.82	0.486
	Diastolic	87.18±10.79	90.30±16.69	0.193
	Glucose (Mean ± SD)	163.44±62.10	167.40±96.11	0.215
CT-scan report (N, %)	Normal	54 (98.18%)	159 (86.41%)	<0.0001
	Hypodensity<1/3 Hemisphere	1 (1.82%)	19 (10.33%)	
	With Stroke symptoms	0	6 (3.26%)	

mean age, weight and distribution of patient according to gender and underlying diseases in the two groups (P>0.05). The mean blood glucose level and systolic and diastolic blood pressure in the two groups were not significantly different at admission time (P>0.05). The frequency of patients with abnormal CT-scan response (less than one-third of hemispheres or stroke symptoms) was significantly higher in the control group (P <0.05) (Table **1**).

In control group, 168 patients (91.3%) due to delayed referral, 14 patients (6.6%) due to contraindication for prescribing of tPA, 2 patients (1%) because of dissatisfaction did not receive tPA. There was no significant difference between the two groups in the mean elapsed time from the referral of patients to the hospital to performing CT-scan (Door to CT) (P>0.05). The mean duration of symptoms before arrival to hospital and performing diagnostic measures (Event to CT) in the tPA receiving group was significantly lower than that in the control group (P<0.0001), so that delay in the visiting time to the clinic and loss of golden time was one of the main reasons for not receiving tPA drug in the control group.

However, the mean hospital stay was less in the patients treated with thrombolytic therapy than that in the control group, but there was no significant difference between the two groups (P>0.05) (Table **2**).

At the time of admission and discharge, there was no significant difference between the mean score of NIHSS in the two groups (P>0.05). The mean difference and the decrease in NIHSS score 24 hours after admission and discharge in tPA group was significantly higher (P <0.0001). Moreover, the difference in mean and NIHSS scores at the time of discharge (as compared to admission) was considerably higher in the tPA group than that in the control group (P <0.0001). The mean change and decrease in NIHSS scores were modest and very low in the control group (Table **3**).

At the time of discharge, the mean score of mRS in patients treated with thrombolytic was lower than that in the control group, but there was no significant difference between the two groups (P >0.05). Three months after treatment, the mean scores of mRS in patients treated with thrombolytic were significantly lower than that in the control group (P <0.05) (Table **4**).

The percentage of patients with bleeding complications during the hospital stay in thrombolytic patients (7.27%) was more than that in the control group (4.89%). In the group receiving tPA, one patient (1.82%) suffered from an asymptomatic cerebral haemorrhage, 2 patients (3.64%) suffered from a symptomatic cerebral haemorrhage, and 1 patient (1.82%) suffered from symptomatic gastrointestinal haemorrhage.

Table 2: The Interval between the Onset of Symptoms, Referral to the Hospital, and Receiving tPA

Different time points	tPA	Control	P-value
Door to CT (minutes)	14.19±4.12	15.64±3.81	0.512
Door to Needle* (minutes)	39.0±19.73	-	-
Event to Needle# (hrs)	2.09±0.85	-	-
Event to CT (hrs)	1.45±0.86	15.17±14.51	<0.0001
Duration of hospitalization (day)	5.82±3.34	6.06±3.29	0.651

*The interval between the referral of patients to the hospital and the time taken to administer a thrombolytic agent.
#The interval between symptom onset and the time taken to administer a thrombolytic agent.

Table 3: NIHSS Score at the Time of Admission, 24 Hours after Treatment, and Discharge

	NIHSS	tPA	Control	P-value
Different time points	Time of Admission	11.60±6.45	8.72±6.61	0.057
	24 hours after treatment	10.17±7.02	7.64±5.59	0.004*
	Time of Discharge	7.33±6.59	7.16±5.61	0.865
Mean difference	24 hours after treatment	-2.13±3.65	-0.88±0.52	<0.0001*
	Time of Discharge	-5.80±4.32	-0.39±2.10	<0.0001*

Table 4: The Mean Score of mRS at Discharge Time and 3 Months after Treatment in the Two Groups

mRS (Different time points)	tPA	Control	P-value
Time of Discharge	1.88±1.63	2.17±1.36	0.211
3 months after treatment	1.18±1.42	2.01±1.52	0.001*

Table 5: Rate of Mortality in the Two Groups

Mortality	tPA (n=55)	Control (n=184)	P-Value
Duration of hospitalization	2 (3.64%)	3 (1.63%)	<0.0001
3 months after treatment	4 (7.27%)	14 (7.61%)	0.902

The percentage of deaths during the hospital stay in thrombolytic patients (3.64%) was higher than that in the control group (1.63%). The percentage of patients died three months after treatment in two groups was almost similar (7.27% in the tPA group and 7.61% in the control group) (Table **5**). Both patients who died during hospitalization received medication more than 3 hours after the onset of symptoms. Of the 4 patients died 3 months after treatment in the intervention group, 2 patients received medication less than 3 hours after the onset of symptoms and 2 patients received medication more than 3 hours after the onset of symptoms.

DISCUSSION

In the present study, 168 patients (91.3%) due to delayed referral, 14 patients (6.6%) due to the prohibition of drug use, and 2 patients (1%) because of dissatisfaction did not receive tPA. In the study of Hatamabadi *et al*., 104 (70.3%) patients due to loss of golden time, 31 patients (20.9%) due to the prohibition of drug use, and 8 patients (4.5%) due to lack of specific care beds, and 5 patients (3.4%) due to lack of financial resources missed thrombolytic treatment [26]. In the study of Mojdehipanah *et al*., the most common inhibitory factor in drug intake included delayed visit of neurologists (75%), delayed visits to medical centres (67%), delays in preparation of results of tests (46%), delays in emergency medical visits (39%), delayed CT-scan preparation (36%), antiplatelet drugs (35%), and anticoagulants (26%) [27]. In the study of Nikkhah *et al*., 85.6% of patients did not receive tPA due to delays in a referral [28].

The mean of the onset of symptoms to referral to hospital in the tPA group was significantly lower than that in the control group (P <0.0001), so that the delay in visiting time and the loss of golden time was one of the main reasons for not receiving the tPA in the control group. In a study by Ghadimi Farah *et al*., the duration of the onset of symptoms until reaching the emergency in the treatment group was 89 minutes and in the control group was 331 minutes [30]. At the time of discharge, the mean score of NIHSS in the tPA group was significantly decreased (P>0.05). In the study by Ghadimi Farah *et al*., the mean NIHSS in the tPA group before treatment was 10.8 and the third day after treatment was 9.6 and in the control group, the mean NIHSS before treatment was 16.95 and the third day after treatment was equal to 17 [30]. The study of Ghadimi Farah *et al*. was consistent with the results of the present study in terms of reduction in the NIHSS score after treatment in the tPA group.

The mean difference and the decrease in NIHSS score 24 hours after admission and discharge in tPA group was significantly higher (P<0.0001), indicating a greater reduction in neurological disabilities than before treatment in the intervention group (P<0.0001). Also, the mean difference and the decrease in NIHSS scores during discharge (compared to admission) in the tPA group was significantly higher than that in the control group (P<0.0001). In the study of Ghadimi Farah *et al*., the mean difference between NIHSS before treatment and three days after treatment in the tPA group was 1.2, and in the control group, it was -0.05 (30). In the study of Zarei *et al*., NIHSS score decreased significantly 24 hours after treatment in both groups, but the difference was higher in patients receiving tPA [29]. At the time of discharge, although the mean score of mRS in patients undergoing thrombolytic therapy was lower than that in the control group, the difference was not significant (P>0.05). Three months after treatment, the mean scores of mRS in the tPA group were significantly lower than that in the control group (P

<0.05). In the study of Mahmoudi *et al*., the mean basic mRS was not significantly different between the two groups, but it was significantly lower in the tPA group in the first week and the third month [31]. In the study of Ghadimi Farah *et al*., the mean mRS after 3 months of starting treatment was 2.9 in the tPA group and 4 in the control group (30). The results of the Hacke *et al*. showed that a higher percentage of patients in the treatment group (52.4%) compared to the placebo group (45.2%) had a favourable outcome (mRS 0-1 in 90 days) [32], which were consistent with the results of the present study. In the present study, the percentage of patients with bleeding complications during the hospital stay in patients undergoing thrombolytic therapy was more than that in the control group. Moreover, the percentage of patients who died during the hospital stay in patients undergoing thrombolytic therapy was more than that in the control group. The percentage of patients died three months after treatment in two groups was almost close. In the study of Mahmoudi *et al*., the mortality rate in the treatment group was 29.1% and in the control group was 19.3%, which was not significantly different [31]. In the study of Ghadimi Farah *et al*., 7 cases in the treatment group and 6 ones in the control group died, and the mortality rate was equal in the two groups [30]. In the study of Zarei *et al*., mortality and complications were similar in the two groups [29]. In the study of Nikkhah *et al*., all treated patients were alive three months after treatment [28]. In the study of Sadeghi Hokmabadi *et al*., in subjects undergoing thrombolytic therapy, the mortality rate was 6% in the first 7 days and 23.4% in the first 3 months [24]. In a study by Marier *et al*., the mortality rate in the three months was 17% in patients undergoing thrombolytic therapy and 21% in the control group, which did not show a significant difference [33]. In Clark *et al*., after 90 days, the mortality rate in the placebo group was 6.9%, and in the rt-PA group, it was 11%, which was not significantly different [34]. The Hacke *et al*. study did not show a significant difference in mortality between the two groups (7.7% in the treatment group vs. 8.4% in the control group) [32].

CONCLUSION

Based on the results obtained, due to the presence of multiple inhibitory factors, a small percentage of patients were receiving tissue plasminogen activator. The most important barrier to timely initiation of thrombolytic therapy is the loss of golden time, and public education can be effective in reducing this time lag. Patients with AIS under venous thrombolytic therapy with tPA, who were admitted at a short time from the onset of symptoms, showed improvement in functional measurements and neurological outcomes compared with the control group, so that changes and decreases in neurologic disability were based on the NIHSS score was significant in the treatment group and was very minor in the control group. Also, the significant difference in mRS scores for 3 months after treatment was significantly improved in patients undergoing thrombolytic therapy compared to the control group. Lack of significant difference in the rate of complications and mortality between the two groups indicated the safety and high efficacy of thrombolytic therapy in patients with AIS.

ABBREVIATION

tPA = Tissue plasminogen activator

AIS = Acute ischemic stroke

NIHSS = The National Institutes of Health Stroke Scale

mRS = The modified Rankin Scale

CT = Computed Tomography

SITS = The safe implementation of treatment in stroke

DECLARATION

Ethics Approval

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.REC.1397.585).

Consent for Publication

This manuscript has not been published and is not under consideration for publication elsewhere in whole or in part. No conflicts of interest exist in the submission of this manuscript, and the manuscript has been approved for publication by all listed authors.

Availability of Data and Material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing Interests

None of the authors has any financial and personal relationships with other people or organizations that

could potentially and inappropriately influence this work and its conclusions. Authors declared no competing interest in publishing this paper.

Funding

The study was financially supported by Ahvaz Jundishapur University of Medical Sciences (Grant.No.: U-97160).

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Received on 09-10-2019 Accepted on 12-02-2020 Published on 15-05-2020

DOI: https://doi.org/10.6000/2292-2598.2020.08.02.2