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Original Article

Comparison of Efficacy and Complication of Alteplase Injection in Acute Ischemic Stroke

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Abstract

Background and Aim: Alteplase is a thrombolytic drug that is produced by recombinant DNA technology. Tissue plasminogen activator enzyme which converts plasminogen to the active form of plasmin is also produced by the same technology; it causes fibrinolysis and clot dissolution. This study aimed to compare the efficacy and complications of Alteplase injection in patients with acute ischemic stroke (AIS) during the first 3 hours and 3-4.5 hours after the onset of symptoms.

Methods: In this study, patients with AIS who were referred to Golestan Hospital of Ahvaz city during 2018-2019 were selected. Information was collected by a checklist.

Results: The results showed that the mean Modified Rankin Scale (mRS) for 3 months and 6 months (p-value: 0.91 for 3 months and p-value: 0.80 for 6 months) and National Institutes of Health Stroke Scale (NIHSS) (p-value: 0.21) were not significantly different between both groups; statistically, no significant relationship was observed between them. The incidence of complications after treatment was almost similar, in both groups.

Conclusion: Finally, it was concluded that complications and efficacy of rt-PA (Alteplase) injection were not statistically different, between the two groups under study.

Keywords: Alteplase; Acute Ischemic Stroke (AIS); Side Effects; Treatment; Timing.

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Introduction

Stroke is the third leading cause of death and the most common debilitating neurological disease (1). Ischemia causes neuronal damages and clinical symptoms due to the deprivation of brain tissue in the use of oxygen and glucose as well as metabolic products; if it prolongs, permanent and irreversible neurological damages occur (2). Despite the high prevalence and debilitating effects of stroke, many preventive strategies have been designed. Different treatments for patients are also considered, based on the involved mechanisms of pathogenesis (3). The most important treatments include the use of antiplatelet drugs, anticoagulants, and thrombolytics. The use of these drugs has been able to prevent the progression of the disease to a large extent and improve the clinical symptoms of patients; however, their clinical side effects are a serious problem that can disrupt the treatment process (4).

Alteplase is a recombinant tissue plasminogen activator (rt-PA) is a recombinant thrombolytic drug that causes thrombolysis by activating plasminogen; today, it is prescribed for patients with stroke. Although many studies have been performed about treatment aspects of the Alteplase, a few pieces of research have been done about its efficacy and the side effects (5, 6). Therefore, in

this study, we evaluated the efficacy and side effects of Alteplase usage in patients with stroke.

Methods

This observational cohort study evaluated the patients with acute ischemic stroke (AIS) who were referred to Golestan Hospital of Ahvaz city, during 2018-2019. Based on the interval between the onset of symptoms and referral to the emergency department of a hospital, patients were categorized into two groups; group 1, included patients who referred during the first 3 hours after Symptom onset (n=64), and group 2 the patients who referred within 3.5-5 hours after the onset of symptoms (n=23). rt-PA injection was done for both groups of individuals. Patients with AIS were diagnosed according to the AHA\ASA2018 guideline; the treatment outcomes and complications were compared between the two groups.

After explaining how to conduct the research and the study objectives, the informed consent was signed by patients or their companions. Inclusion criteria included age over 18 years, the onset of symptoms in the last 4.5 hours, and ischemic stroke symptoms. Exclusion criteria were as follows, gastrointestinal or urinary bleeding in the past 21 days, severe head trauma in the past 3 months, Xa inhibitor and low molecular heparin (LMH) intake in the last 24 hours, and intraracial intracranial tumor. Patients' information included demographic characteristics (age, gender), stroke risk factors (hypertension history, diabetes, hypertension, smoking, alcohol or drug use, ischemic heart disease, and history of stroke), blood pressure, and blood sugar. CT scan result, time to onset of symptoms (event to needle), National Institutes of Health Stroke Scale (NIHSS) score at baseline were recorded in the pre-designed checklist.

Patients were selected for thrombolytic treatment and tPA injection based on the AHA/ASA 2018 guideline. tPA was administered at a dose of 0.9 mg/kg and 10% as a bolus, and the rest was infused continuously for 1 hour. Then, the following information was recorded, NIHS score 24 hours after treatment, complications including symptomatic or asymptomatic intracerebral hemorrhage, bleeding in other organs, pneumonia, cardiovascular complications, embolism, allergic reaction, and mortality during hospitalization. Also, 3 months and 6 months after admission, the patient or his companions were contacted by phone, and the Modified Rankin Scale (mRS) and the incidence of morbidity and mortality were evaluated in both groups.

Statistical Analysis

In quantitative variables, mean or median was used to describe the data center; standard deviation (SD) or mid-quarter amplitude was used to describe the data scatter. Frequency and percentage were used in the qualitative variables. Kolmogorov-Smirnov test and quadratic-multiple diagram were applied to check the data normality. For univariate data analysis, the Chi-square test, Fisher's exact test, independent t-test, Mann-Whitney test, and univariate Cox regression were used. The significance level was considered as 0.05. All analyzes were performed using SPSS software version 22.

Results

After selecting patients, 64 of them were treated with rt-PA within three hours after the onset of symptoms; 23 individuals received rt-PA about 4.5-5 hours after the onset of symptoms, too. Patient demographic information has been listed in Table 1. Accordingly, no significant relationship was observed for the studied variables between the two groups.

However, the length of hospital stay was longer in the group which received the drug during the first three hours after the onset of symptoms; the difference was not statistically significant (p-value=0.857) (Table 1).

In the first group, 3.1% of treated patients with rt-PA developed symptomatic cerebral hemorrhage as a complication of thrombolytic therapy. In the other group, 8.7% of patients had an asymptomatic cerebral hemorrhage, which was not statistically significant (p-value=0.284).

Asymptomatic cerebral hemorrhage after treatment was detected in 12.5% of the patients who were categorized in the first group. This complication

did not occur in the patients who received the drug during 4.5-5 hours after the onset of symptoms. However, the difference was not statistically significant between the two groups (p-value=0.103).

Table1. Demographic information of patients

Variables		≤ 3 hours	> 3 hours	p-value
Age (years)		67.75±13.12	66.57±12.73	0.709
Sex	Women	30(46.9)	12(52.2)	0.663
	men	34(53.1)	11(47.8)	
Systolic BP(mmHg)		149.83±28.8	150.17±30.19	0.928
Diastolic BP (mmHg)		87.97±15.35 90(20)	89.09±14.91 90(20)	0.749
Blood Sugar (mg/dl)		138.83±42.79 129(42)	151.17±45.28 142(66)	0.199
NIHSS		14.97±6.59	15.13±7.32	0.922
Days of Hospitalization		8.49±5.52	7.05±4.08	0.857
HTN	No	20(31.3)	9(39.1)	0.492
	Yes	44(68.8)	14(60.9)	
Smoking	No	54(84.4)	17(73.9)	0.267
	Yes	10(15.6)	6(26.1)	
Diabetes	No	47(73.4)	18(78.3)	0.648
	Yes	17(26.6)	5(21.7)	
Atrial fibrillation	No	55(85.9)	21(91.3)	0.720
	Yes	9(14.1)	2(8.7)	
Vasculitis	No	62(96.9)	22(95.7)	1
	Yes	2(3.1)	1(4.3)	
Hyperlipidemia	No	51(79.7)	19(82.6)	1
	Yes	13(20.3)	4(17.4)	
Previous stroke	No	63(98.4)	22(95.7)	0.461
	Yes	1(1.6)	1(4.3)	
Congestive heart failure	No	49(76.6)	17(73.9)	0.799
	Yes	15(23.4)	6(26.1)	
Use of anticoagulation	No	60(93.8)	23(100)	0.569
	Yes	4(6.3)	0(0)	
ACA	No	55(85.9)	21(91.3)	0.720
	Yes	9(14.1)	2(8.7)	
MCAstem	No	50(78.1)	20(87)	0.541
	Yes	14(21.9)	3(13)	
MCA superior	No	35(54.7)	16(69.6)	0.214
	Yes	29(45.3)	7(30.4)	
MCAinferior	No	40(62.5)	11(47.8)	0.220
	Yes	24(37.5)	12(52.2)	
Lacunar	No	63(98.4)	22(95.1)	0.461
	Yes	1(1.6)	1(4.3)	
PCA	No	58(90.6)	19(82.6)	0.694
	Yes	6(9.4)	2 (17.4)	

Abbreviation: BP: Blood pressure, NIHSS: National Institutes of Health Stroke Scale, HTN: Hypertension, ACA: Anterior Cerebral Artery, MCA: Middle Cerebral Artery, PCA: Posterior Cerebral Artery.

In addition, 25% of patients in the first group experienced other complications (subarachnoid, epidural, subdural hemorrhage, extracranial hemorrhage, embolism, allergic reaction, Petechia, pneumonia, arrhythmia, and myocardial infarction);

the incidence of these complications was 13% in the second group.

Statistical analysis showed no significant differences between the studied groups (p-value=0.378) (Table 2).

Table2. Related side effects of rt-PA injection after the treatment in patients

		Univariable		
		≤ 3 hours	**> 3 hours**	**p-value**
Symptomatic ICH	No	62(96.9)	21(91.3)	0.284
	Yes	2(3.1)	2(8.7)	
Asymptomatic ICH	No	56(87.5)	23(100)	0.103
	Yes	8(12.5)	0(0)	
Other side effects*	No	48(75)	20(87)	0.378
	Yes	16(25)	3(13)	

ICH: Intracerebral hemorrhage. * Subarachnoid hemorrhage, epidural, subdural, extracranial hemorrhage, embolism, allergic reaction, petechia, pneumonia, arrhythmia, and myocardial infarction.

Patients were divided into two groups in terms of mRS score with favorable (score zero and one) and unfavorable outcomes (score 2, 3, 4, 5, and 6). Statistical evaluation of mRS score including the calculation of OR and CI was done, at the times three and six months after treatment in the patients of the two groups; no statistically significant difference was found between the groups. The results are shown in Table 4.

Comparison of Hazard Ratio (HR) showed a similar risk between the two groups in terms of mortality during hospitalization up to six months and after thrombolytic therapy (Table. 3).

Table3. Mortality-derived treatment in patients

	Univariable			Multivariable		
	HR	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Time($\geq$ 3 h to $<$ 3 h)	1.21	(0.23 − 6.30)	0.818	1.61	(0.15 − 17.60)	0.696

Table 4. mRS score at 3 and 6 months after acute stroke in patients.

	Univariable			Multivariable		
	OR	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
mRS 3month	1.04	(0.24 − 4.58)	0.955	0.90	(0.15 − 5.57)	0.911
mRS 6month	1.07	(0.26 − 4.31)	0.926	0.80	(0.14 − 4.76)	0.809

mRS: modified Rankin scale

It was also found that the mean NIHSS before treatment was lower in the patients of group one, but this difference was not statistically significant (p-value = 0.922). After treatment, the mean NIHSS was 10.55 ± 7.76 in the first group, and it was 11.83 ± 9.44 in the other; it was not statistically significant, too (Table.5).

Table 5. Mean NIHSS score after treatment in patients.

	Univariable			Multivariable		
	≤ 3houre	> 3 houre	p-value	B	95%CI	p-value
NIHS Score	10.55±7.76	11.83±9.44	0.524	1.56	(−0.91 − 4.04)	0.212

Discussion

The side effect of rt-PA in patients with AIS is highly time-dependent (7). Extending the time for intravenous rt-PA in patients with AIS is an important strategy in stroke patients' thrombolytic therapy (8). Rapid administration of rt-PA after stroke improves the outcomes of patients' clinical conditions (9). In a study, the rate of patients treated with IV rt-PA during the first 3 hours and 4.5 hours was examined; it was found that the majority of patients were treated within 0-3 hours but increasing the duration to 3-4.5 hours does not appear to affect patient outcomes adversely (10). In the present study, the results showed that the mean NIHSS after treatment was lower than before, in both groups. However, the mean NIHSS after treatment in both groups was almost the same. Therefore, no statistically significant relationship was observed between them. Also, the mean score of mRS was similar in both groups and no significant difference was observed between them.

Symptomatic Cerebral hemorrhage in the patients treated with rt-PA about 3 hours after the onset of symptoms (3.1%) was less than the other group (8.7%,); it was not statistically significant (p-value = 0.284). This result indicates the importance of diagnosing the signs and symptoms of a stroke by patients or their families and getting the patient to the hospital quickly. Also, Shobha et al. examined the effect of thrombolytic therapy on patients with AIS; they reported that rt-PA intake increased symptomatic intracerebral hemorrhage significantly, in individuals who received the drug during 3–4.5 hours compared to ones who received within 0–3 hours (11). As these results, Xu et al.'s study showed that the rate of asymptomatic cerebral hemorrhage within 24-36 hours, mortality rate, and NIHSS were not significantly different between the two groups (0–3 and 3–4.5 hours) (7). In line with this study, asymptomatic cerebral hemorrhage was found in 12.5% of treated patients with rt-PA about 3 hours after the onset of symptoms, but it did not occur in the other group; no evidence was found to confirm the significant statistical difference between the two groups.

Hacke et al. examined the effect of Alteplase and placebo 3-4.5 hours after AIS; they showed that intracranial hemorrhage was significantly greater in Alteplase receivers (12). Clark et al. evaluated the effect of rt-PA during 3 and 5 hours after symptom onset, in a clinical trial study. They stated that the symptomatic intracerebral hemorrhage rate increased significantly within the first 10 days of treatment with rt-PA (13). In this study, 25% of rt-PA treated patients during the first 3 hours after the onset of symptoms, and 13% of the subjects in the other group experienced the subarachnoid, epidural, subdural hemorrhage, extracranial hemorrhage, embolism, allergic reaction, petechia, pneumonia, arrhythmia, and myocardial infarction.

Conclusion

The present study showed that rt-PA prescription after 3 hours from the onset of symptoms is not much different in terms of complications occurrence, in comparison to patients with AIS who receive drug earlier. Therefore, it is better to focus on this issue in future studies. We recommend a survey in the larger population. Therefore, to confirm a definite achievement, other centers should perform similar studies in the field of thrombolytic treatment of patients with AIS.

Conflict of Interest

The authors declared that they have no conflict of interest.

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Not declared.

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Ethics

This study was approved by the Ethics Committee of the Vice Chancellor for Research of Ahvaz Jundishapur University of Medical Sciences (Ethics approval ID: IR.AJUMS.REC.1398.923.

All the procedures performed in this study, involving human participants were following ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences as well as the Helsinki declaration. Written informed consent was obtained from all participants in this study.

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