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Outcome of Treatment with Intravenous Alteplase in Acute Stroke Patients

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ABSTRACT

Background and Objective: Stroke is one of the main causes of death and disability in the world, and its treatment includes the re-supply of blood to the brain tissue using different methods, including alteplase injection. The aim of this study is to determine the outcome of treatment with intravenous alteplase.

Methods: This cross-sectional study was conducted on all stroke patients referred to Babol Rouhani Hospital in 2019-2021. Patients were divided into two groups receiving intravenous alteplase and routine and supportive treatment groups. Demographic information and the scores of National Institutes of Health Stroke Scale (NIHSS) to evaluate the improvement of stroke symptoms and Modified Rankin Scale (mRS) to evaluate the severity of disability in three periods of 7, 30 and 90 days were investigated and compared.

Findings: Out of 100 studied patients, 49 people were in alteplase group and 51 people were in routine and supportive treatment group. In examining the NIHSS scale of patients in three follow-up periods, there was a significant difference in the alteplase group compared to the routine and supportive treatment group ($p<0.001$). Moreover, regarding the mRS scale, on the 90th day (0.65±0.80 vs. 1.55±1.11) unlike the 30th day (1.65±1.07 vs. 1.31±0.92), there was a significant difference between the two groups receiving alteplase and the routine and supportive treatment group ($p<0.001$).

Conclusion: The results of the study showed that treatment with intravenous alteplase can have a suitable effect on neurological disorders after a stroke and can improve the level of disability in daily functioning in the long term, up to the 90th day of patient follow-up.

Keywords: *Stroke, Tissue Plasminogen Activator, Alteplase, Disability Assessment, National Institutes of Health (NIH).*

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Introduction

A stroke occurs as a result of arterial blockage or narrowing, followed by insufficient blood supply to the brain tissue and ischemia. This disease is one of the most important causes of death and disability in the world (1). Two-thirds of strokes occur in developing countries, such as Iran (1-6). Various correctable and non-correctable factors such as high blood pressure, diabetes mellitus, obstructive heart disease, gender and race are effective on this disease (7-9). To diagnose this disease, we can use both CT Scan (Computed Tomography) and MRI (Magnetic Resonance Imaging). CT Scan is usually the first step in diagnosis because MRI is much more expensive and takes more time; But MRI is a more sensitive and accurate method to diagnose the acute ischemic form of stroke. Of course, things like CTP (Perfusion CT) and CTA (CT Angiography) can gradually replace MRI (10, 11).

More than two decades ago, it was observed how the outcome of patients suffering from ischemic stroke with endovascular therapeutic interventions and mechanical thrombectomy lead to significant recovery from death and severe disability. Rapid return of blood supply in any way is practically the best treatment. In addition to paying attention to this importance, other things can increase the chances of treatment with maximum success, which include proper diagnosis, proper hemodynamic regulation, checking the risk of complications and preventing them, considering the time factor and emergency medicine specialists (12).

One of the irreplaceable treatments introduced for this disease is treatment with rtPA as quickly as possible after diagnosis (12). The time of receiving the drug is very important in the response to the treatment. As a result, if the patient receives rtPA within the first three hours of the onset of symptoms, his/her functional problems will decrease by less than 50% within three months (13-15). This drug has complications such as symptomatic intracerebral hemorrhage (sICH) (16). This drug showed very good results in the recovery of stroke patients following its use in studies conducted on 624 patients (15). Since then, this drug has been subjected to various trials and has been able to stabilize its position.

Since intravenous rtPA has been used in the stroke center in Babol for several years, and no study has been conducted on the results and consequences of using intravenous alteplase in this center, therefore, this study was conducted to determine the outcome of stroke patients referred to the stroke center of Ayatollah Rouhani Hospital in Babol, who were treated with or without intravenous rtPA.

Methods

This cross-sectional study was conducted on stroke patients referred to Ayatollah Rouhani Hospital between 2019 and 2021 after being approved by the Ethics Committee of Babol University of Medical Sciences with code IR.MUBABOL.REC.1399.286. The study samples were selected by census sampling method. Of all the patients who came to the hospital with acute stroke complaint, 100 people were included in the study. In order to confirm the diagnosis of stroke and determine its type (ischemic or hemorrhagic), an emergency CT scan was requested and performed. Based on the time elapsed since the onset of symptoms and the type of stroke, the type of treatment was chosen:

- Patients diagnosed with ischemic stroke less than 4 and a half hours after the onset of their symptoms, aged 18 years and older and with blood pressure less than 185/110, were treated with intravenous alteplase.
- Patients whose visit time was more than 4 and a half hours or had one of the contraindications of alteplase (hemorrhagic stroke, history of acute ischemic stroke in the last 3 months, history of severe concussion in the last 3 months, intracranial or intraspinal surgeries in the last 3 months, history of cerebral hemorrhage,

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history of gastrointestinal malignancy or gastrointestinal bleeding in the last 21 days, coagulopathy [PLT< 100000, INR> 1.7, aPTT> 40 or PT> 15], use of LMWHs in the past 24 hours, and intra-axial/intracranial neoplasms), were treated with antiplatelet (ASA and clopidogrel) and supportive measures.

Research tools: The National Institutes of Health Stroke Scale (NIHSS) is a questionnaire developed by federal, international, commercial, and scientific organizations. This questionnaire is intended to improve the health and care of stroke patients. In the neurological examination, eleven assessment questions for consciousness, vision, sensation, movement, speech, and language are administered to assess various aspects of brain function. A score of 0 or 4 is assigned to each item, where 0 indicates normal performance and 4 indicates total functional impairment. A person can receive a score of 42, which represents the most severe stroke-related condition. In studies, the NIHSS plays a vital role where objective evaluation of the effectiveness of various stroke treatments and rehabilitation strategies is possible. As a result, researchers can use standardized criteria to determine whether stroke treatment is beneficial (17). The Modified Rating Scale (mRS) is commonly used to measure the level of disability or dependence of people suffering from stroke or other neurological disorders. mRS is the most common outcome measure in stroke studies. Based on this scale, the score ranges from 0 to 6, from asymptomatic to fatal (18). Patient information, including age, sex, NIHSS scores after treatment on 7^{th}, 30^{th}, and 90^{th} days to assess the improvement of stroke symptoms, and mRS scores in 1-month and 3-month follow-ups to assess the severity of disability or mortality status, is recorded in a checklist.

The data were statistically analyzed using SPSS version 22. The variables of the research were described by reporting the statistical indicators of mean, standard deviation, frequency and percentage. The analysis of the studied data was done using Chi-square or Fisher's exact statistical tests, independent and paired t-tests, and repeated measures ANOVA in a significance level of $p<0.05$.

Results

Out of 100 patients with acute stroke, 49 were in the target treatment group and 51 were in the routine and supportive treatment group. The time from the onset of symptoms to receiving treatment was 167.69±71.32 minutes. The mean age, gender and number of people in terms of occurrence of cerebral hemorrhage during 7 days after treatment were reported in total samples and separately based on treatment groups (Table 1).

Table 1. Description of treatment groups based on research variables

Variable	Total samples (n=100) Mean±SD or Number(%)	Treatment group		p-value
		Alteplase (n=49) Mean±SD or Number(%)	Routine and supportive treatment (n=51) Mean±SD or number (%)	
Age	66.81±11.77	66.73±11.94	66.90±11.71	0.94*
Gender				
Male	51(51)	26(53.06)	25(49.02)	0.83**
Female	49(49)	23(46.94)	26(50.98)	
Bleeding				
Yes	10(10)	6(60)	4(40)	0.463***
No	90(90)	43(47.8)	47(52.2)	

*Independent t-test, **Chi-square test, ***Fisher's exact test

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The mean age of all patients was reported to be 66.81±11.77 years, and the two treatment groups were homogeneous in terms of mean age (p=0.940). 51 (51%) of the patients were male and 49 (49%) were female, and no significant relationship was observed between gender and treatment with or without intravenous alteplase (p=0.830). Among the patients, ten patients had a bleeding complication during the 7-day period after the treatment, 6 of them (60%) received alteplase and 4 (40%) received routine and supportive treatment, and there was no significant relationship between the bleeding complication and the type of treatment.

The mean score of NIHSS (disability level) on the 7th, 30th, and 90th days of follow-up in patients receiving intravenous alteplase and patients receiving routine and supportive treatment has been reported and compared (Table 2).

Table 2. NIHSS score on the 7th, 30th and 90th days of follow-up in two treatment groups

Groups	NIHSS score at follow-up			p-value*
	7th day Mean±SD	30th day Mean±SD	90th day Mean±SD	
Alteplase	4.92±3.08	2.90±2.55	1.84±2.37	<0.001
Routine and supportive treatment	4.43±2.49	4.39±2.88	4.57±3.28	0.54
p-value**	0.38	0.007	<0.001	

*Repeated Measures ANOVA test with Greenhouse-Geisser correction, **Independent t-test

The results show that the disability score based on the NIHSS criteria in the follow-up on the 7th day, 30th day, and 90th day for the group that was treated with alteplase had a significant decreasing trend (p<0.001). In the following, using a post hoc test with Bonferroni correction, it was determined that the score of stroke symptoms on the 30th day compared to the 7th day decreased by 2.02 and on the 90th day compared to the 37th day by 1.06 and 3.08, respectively, and this decrease has been significant. However, in the group that received routine and supportive treatment, there was no significant difference in the level of disability based on NIHSS in the follow-up on the 7th day, 30th day, and 90th days. According to these results, it can be said that alteplase drug has a significant effect in reducing the level of disability and improving the symptoms of acute stroke, but routine and supportive treatment showed no significant effect in reducing the level of disability.

Regarding the difference in NIHSS scores in the two treatment groups in each of the follow-ups, the mean NIHSS score in the first (p=0.007) and third month (p<0.001) was different and was significantly lower in patients who received alteplase. However, on the seventh day after receiving the treatment, no significant difference was observed in the mean values.

The mean score of mRS (severity of disability and dependence) in the 30th and 90th days of follow-up in patients receiving intravenous alteplase and patients receiving routine and supportive treatment has been reported and compared (Table 3).

In the group that received alteplase, the mRS score on the 90th day was reduced compared to the 30th day, and the score difference was significant in the two follow-up sessions (p=0.02). The significance of this difference was also observed in the follow-up mRS scores in the first and third month (p<0.001), with the difference that the score related to the severity of disability in the third month was calculated 0.24 units higher.

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The mean mRS score on the 30th day for the patients who received alteplase was higher than the routine and supportive treatment group, but the difference was not significant, while on the 90th day of follow-up, the mean mRS score in the patients receiving alteplase was lower than the second group and the difference was significant (p<0.001).

Table 3. mRS score on the 30th and 90th days of follow-up in two treatment groups

Variable	mRS score at the time of follow-up		p-value*
	30th day Mean±SD	90th day Mean±SD	
Alteplase	1.65±1.07	0.65±0.80	0.02
Routine and supportive treatment	1.31±0.92	1.55±1.11	<0.001
p-value**	0.93	<0.001	

*Paired t-test, **Independent t-test

Discussion

The mean age of the patients in the present study in the two groups was over 65 years, which has been confirmed in other studies. In a study by Hosseininezhad et al., 90% of stroke patients were over 60 years old (19). The study of Chang et al. also showed that the incidence of stroke increases with age, and two-thirds of stroke cases occur in people over 65 years old (20). Aging is associated with the acceleration of stroke risk factors over a long period of time, which ultimately leads to an increased risk of stroke. For example, high blood pressure and diabetes, which are among the most common risk factors for vascular diseases, are more prevalent in the elderly, which itself is one of the factors that justify the occurrence of stroke at older ages (21).

In this study, only ten people experienced bleeding problems during the first week. This result is consistent with the review of Chen et al., a study that retrospectively evaluated patients treated with alteplase and reported a significant risk of bleeding in the first 24 hours of treatment (22). In most of the studies that have been conducted in the field of the performance of thrombolytics in stroke, the amount of short-term consequences of this drug has been taken into account, which even in some studies has led to a poor performance of this treatment (23); in the study of Gao et al., patients who received rtPA and patients who received thrombolytic drugs showed a significant relationship in terms of NIHSS in the short term, and this showed that patients who received rtPA had fewer complications compared to patients who received thrombolytics (24).

In the present study, the mean NIHSS score decreased over time, and in other words, the neurological clinical outcomes in the patients receiving alteplase in the 90-day period were better than those in the routine and supportive treatment group. In regard with the mRS questionnaire, a significant difference was found between the two groups on the 90th day in the current study.

This finding is similar to the study of Khatri et al. comparing the outcomes of alteplase and aspirin use in patients. They reported that the mean NIHSS score at the beginning of the study was significantly lower than at the 90-day follow-up (25). Wardlaw et al. conducted a study to investigate the results of rtPA treatment in patients with stroke and showed that thrombolytic treatment can lead to better treatment outcomes, which is in line with the results of the present study (14). In addition, in the study of Hacke et al., which was similar to our study, it was observed that in the alteplase group, the number of patients who had

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a significant recovery was more than in the placebo group, while there was no difference in the mortality rate between the groups. Their study concluded that the use of alteplase in the period of 3 to 4 and a half hours after the onset of symptoms causes a significant improvement in the symptoms and outcome of patients (26). In the study of Sari et al., they found a significant decrease in the mRS scale in the three-month study of treatment with thrombolytic drugs (27). In the study of Dong et al., they stated that in the interval of three months after thrombolytic therapy, the score of NIHSS and mRS questionnaires had decreased significantly, which indicates a better clinical outcome in these patients, and the outcome of patients treated with intravenous rtPA may be related to different vascular risk factors associated with different types of stroke (28).

In the present study, the mean score of NIHSS and mRS questionnaire in the alteplase group on the 90th day of the study was found to be significantly lower than the routine and supportive treatment group, which confirmed the better prognosis in 90-day clinical outcomes in the alteplase group.

Conflict of interest: The authors declare that they have no competing interests.

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