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Research Paper: The Outcome of Treatment With Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke

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Running Title r-TPA in Acute Ischemic Stroke and Outcome

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ABSTRACT

Background: Thrombolytic therapy is the recommended treatment of acute ischemic stroke. It is crucial to evaluate the treatment results with recombinant Tissue Plasminogen Activator (r-TPA) in patients with acute stroke.

Objectives: This study aimed to evaluate treatment outcomes with r-TPA in patients with acute stroke in a referral stroke center in Iran.

Materials & Methods: In this retrospective study, 87 patients with symptoms of acute stroke were examined. They were referred to a stroke center in Gilan Province, Iran, from June 2016 to April 2020 and received r-TPA (0.9 mg/kg). Demographic information, the time interval between the onset of symptoms and r-TPA administration, complications, and National Institutes of Health Stroke Scale (NIHSS) upon arrival and discharge and death of patients were extracted from their hospital files. The paired t-test, independent t-test, and Pearson correlation test were used to compare variables using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

Results: The Mean±SD of NIHSS reduced from 14.7±6.4 to 8.9±7.6 (P<0.001). The most common complication was Intracerebral Hemorrhage (ICH) (12.6%). The hospital mortality rate was 23%. ICH occurred among 40% (n=8) of those who expired, and 4.47% (n=3) of them survived, and this difference was significant (P<0.001).

Conclusion: The recovery with r-TPA administration in the stroke center was acceptable. Mortality and ICH occurrence rates were higher than other non-Iranian studies. It seems that we should change the case selection criteria and prescription dose to achieve better results of treatment with TPA.

Keywords: Tissue plasminogen activator, Stroke, Thrombolytic therapy

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Highlights

- The National Institutes of Health Stroke Scale (NIHSS) score of the stroke patients receiving recombinant Tissue Plasminogen Activator (r-TPA) decreased significantly.
- The mortality rate of the stroke patients who received r-TPA was 23%.
- Intracerebral hemorrhage was the most common complication among stroke patients who received r-TPA.

Introduction

A stroke is a vascular event with serious health consequences [1]. It is an acute disease that arises from the sudden loss of blood supply to brain vessels [2]. Stroke mainly occurs in older adults and has been one of the most concerning health issues with an increase in the aging of human societies [3]. Stroke also is the most common cause of disability [4]. Annually, stroke occurs in 500000 people for the first time, and 100000 people as a recurrent stroke. Besides, it is one of the risk factors of mortality among approximately 160000 people [5]. Stroke is a manifestation of recent coronavirus infection, too [6-8].

The prevalence of this disease is 372 per 100000 people in Iran, according to Dalvandi et al.'s study [9]. This prevalence is significantly higher than that in most of the Western countries [9, 10]. The prevalence and mortality of this disorder are high, so that it is the third leading cause of death in the world and the second leading cause of death in Iran after cancer and cardiovascular diseases [11].

Among the patients, who survived the acute phase, 50% live for more seven years, among whom 10% develop no disability, 40% moderate disability, 40% severe disability, and 10% need permanent care in medical centers. Therefore, the purpose of care is to prevent re-attack, treat complications, improve the patients' quality of life, and reduce the costs and dependence of patients [12].

The recommended treatment of acute ischemic stroke is using thrombolytic agents, including recombinant Tissue Plasminogen Activator (r-TPA). It could partially or entirely relieve the symptoms. r-TPA is a serine protease (enzymes that cleave peptide bonds in proteins) with the corresponding gene on chromosome 8 (8P12) in humans. It catalyzes the conversion of plasminogen to plasmin. This property is the reason for its ability to decompose fibrin-containing clots [13-15]. Interleukin-6, an essential inflammatory molecule in stroke [16], decreases significantly after using r-TPA in an animal model of stroke [17]. Previous studies indicate that r-TPA treatment may effectively improve neurological impairment in patients with acute ischemic stroke [18, 19]. Prescription of r-TPA, 3 to 4.5 hours after the onset of symptoms, improves clinical outcome and performance in patients with acute ischemic stroke [20, 21].

There has been an increasing trend in using this treatment—one study in Australia aimed at assessing the rate of using r-TPA in 103970 patients with acute stroke. The researchers found that using r-TPA has increased from 9.9% in 2006 to 21.8% in 2018, and this trend is expected to reach 24% by 2025 [22].

Treatment with r-TPA needs attention to its risks and benefits as bleeding is the most common side effect that may limit using r-TPA despite the instruction recommendations [22-28]. Therefore, identifying patients at risk in the acute phase is essential to prevent neurological deterioration and predict outcomes in acute ischemic stroke under treatment of venous thrombolysis. This study aimed at evaluating the outcome of treatment with r-TPA in an academic center in the north of Iran as a stroke center in Gilan Province and determining influential factors in predicting favorable or unfavorable outcomes in patients receiving r-TPA.

Materials and Methods

We recruited all stroke patients who received r-TPA in Poursina Hospital as a stroke center in Gilan Province, Iran, from January 2015 to April 2020. The patients were visited in the Emergency Department and took a brain Computed Tomography (CT) scan to check the contraindications of r-TPA therapy. Then, they became candidates for r-TPA administration and received it at a standard dose (0.9 mg/kg). The patients with incomplete files were excluded from the study (exclusion criteria).

Ninety patients were initially included in the study, and then three of them were excluded from the study due to incomplete files. The demographic information, history

of underlying diseases, previous use of anticoagulants, history of smoking and alcohol use, blood pressure and blood glucose at admission, the time interval between the onset of symptoms and prescription of r-TPA and complications, mortality, the score of National Institutes of Health Stroke Scale (NIHSS) [29] at the baseline and discharge were extracted from their medical files.

We presented the treatment results by comparing NIHSS at baseline and discharge. We then measured the prevalence of complications of r-TPA administration, including bleeding and mortality.

Data analysis

We used frequency distribution and percentage indices to describe qualitative information and Mean±SD to describe quantitative information. The paired t-test was used to compare changes of quantitative variables within one group. An independent t-test was used to compare the differences between the groups. The correlation between quantitative variables was also measured using the Pearson correlation test. If the normality assumption was not established, we used the non-parametric equivalent of the tests. We performed data analysis using IBM SPSS for Windows, version 20 (IBM Corp., Armonk, NY, USA). A P value of less than 0.05 was considered statistically significant.

Results

We examined 87 stroke patients receiving r-TPA with a Mean±SD age of 70.40±12.24 years (range: 32-95 years). The baseline Mean±SD blood glucose level of participants was 153.69±62.43 mg/dL. Their Mean±SD of platelet count was 207.11±67.61 per µL, and the Mean±SD International Normalized Ratio (INR) level was equal to 1.02±0.06.

About 59.2% (n=46) participants were male, and 89.7% (n=78) had normal blood pressure (less than 185/90 mm Hg). About 13.8% of participants (n=12) smoked cigarettes, and 1.1% of them (n=1) were alcohol users. Also, 69% of participants (n=60) had a history of hypertension, 35.6% (n=31) hyperlipidemia, and 26.4% (n=23) diabetes mellitus. Furthermore, 14.9% of participants (n=13) had a history of Cerebrovascular Accident (CVA) 3 months before admission. None of the participants received anticoagulants. These results indicated that among participants with complications (n=12, 13.7%), Intracranial Hemorrhage (ICH) was the most common complication (91.7% of complications) with an overall frequency of 12.6% (n=11). Hematuria was the other complication that occurred in only one person. Around 77% of participants (n=67) were discharged and 23% (n=20) expired (hospital mortality). ICH occurred among 40% (n=8) of those who expired and 4.47% (n=3) of those who survived, and the difference was significant (P<0.001).

Table 1. Mean±SD of NIHSS score change of patients with stroke treated with r-TPA

Variables	Subgroups	Mean±SD	Comparative Tests		
		NIHSS Score Change	Evidence	df	P
Gender	Male	-5.44±6.61	0.47	66	0.70
	Female	-6.23±6.95			
Hypertension	Normal	-5.61±6.79	0.57	66	0.83
	Abnormal	-7±6.46			
Hyperlipidemia	Yes	-4.59±7.02	1.02	66	0.31
	No	-6.36±6.57			
Diabetes mellitus	Yes	-6.11±5.72	0.22	66	0.66
	No	-5.68±7.07			
Previous cardiovascular accident	Yes	-5.27±9.03	0.27	66	0.78
	No	-5.89±6.28			
Total score (paired t-test)		-5.79±6.7	7.2	67	<0.001

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Table 2. Results of the correlation between variables and NIHSS in patients with stroke treated with r-TPA

Variables	NIHSS Score Change	
	Correlation Coefficient	P
Age	0.06	0.62
Blood sugar	0.003	0.98
Platelets	-0.01	0.93
International normalized ratio	0.06	0.59
Referral time	0.01	0.94

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Analytical results of NIHSS

The results of the paired t-test indicated that the Mean±SD of total NIHSS score of the participants decreased significantly from 14.76±6.4 to 8.96±7.6 (P<0.001). There was no statistically significant relationship between changes in NIHSS score and sex, history of hypertension, diabetes mellitus, hyperlipidemia, and history of CVA (the independent t-test). Because the number of those who smoke and consume alcohol was low, the effect of these two factors could not be evaluated (Table 1).

The correlation between research variables and NIHSS score

The results indicated no significant correlation between NIHSS score change and age, blood glucose level, platelet level, INR at admission, and the latency time to receive r-TPA. Twenty-nine patients presented with a delay of 3 hours or more in the study, and the mortality rate was 24.1% in this group (Table 2).

The relationship between risk factors, outcomes, and complications

The present study results indicated no statistically significant relationship between patients' underlying factors such as diabetes mellitus, history of hypertension, hyperlipidemia, and history of CVA with its outcomes and complications (P<0.05). Because the number of those who smoke and drank alcohol was low, the effects of these two factors cannot be evaluated (Tables 3 and 4).

Discussion

The present study evaluated the results of treatment with recombinant tissue plasminogen activator in patients with acute stroke. We found that the hospital mortality rate of the participants was 23%. About 13.7% of the participants developed complications, and the most common complication was ICH (12.6%). It occurred among 40% of the expired and 4.47% of the survived patients, and the difference was significant.

The Mean±SD of the total NIHSS score of participants significantly decreased after receiving r-TPA. Twenty-

Table 3. Results of the relationship between underlying factors and outcomes in patients with stroke treated with r-TPA

Underlying Factors	No. (%)		P
	Survived	Expired	
Hypertension	44 (65.7)	16 (80.0)	0.22
Diabetes mellitus	17 (25.4)	6 (30.0)	0.68
Hyperlipidemia	22 (32.8)	9 (45.0)	0.31
History of CVA	10 (14.9)	3 (15.0)	0.99
Total	67 (77)	20 (23.0)	-

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Table 4. Results of the relationship between underlying factors and ICH in patients with stroke treated With r-TPA

Underlying Factors	No. (%)		P
	ICH	ICH	
Hypertension	8 (72.7)	52 (69.3)	0.317
Diabetes mellitus	3 (27.3)	20 (26.7)	0.833
Hyperlipidemia	4 (36.4)	27 (36.0)	0.756
History of CVA	2 (18.2)	10 (13.3)	0.051
Total	11 (12.6)	75 (86.2)	-

nine patients presented with a delay of 3 hours or more in the study, and the mortality rate was 24.1% in this group. The present study results did not indicate any statistically significant relationship between gender, history of hypertension, diabetes mellitus, hyperlipidemia, and history of CVA with consequences and complications. Furthermore, there was no significant correlation between differences in NIHSS with age, blood glucose level, platelet level, INR at admission, and the latency time to receive r-TPA. The results of the present study indicated that the mortality rate of the participants was 23%, which was in agreement with that reported by Sari Aslani et al. (21.7% in-hospital mortality rate) [30]. The Albers et al. study results also indicated that a 30-day mortality rate in patients receiving r-TPA was 13% that was lower than the mortality rate in our study despite the longer follow-up duration [23].

In a meta-analysis by the third International Stroke Trial (IST-3) collaborative group in 2012, the total death from cerebral causes within 7 days was 145 (10%) versus 87 (6%) (OR=1.76 [1.32 to 2.34] P=0.0001). The absolute difference per 1000 was 38 (95%CI: 20 -57) [31].

The mortality rate of 0 in a study by You et al. [27] was much lower than observed in our study. In Huisa et al. study, the mortality rate of patients under the treatment of r-TPA was not significantly different with a group that did not receive thrombolytic therapy (5.1% vs. 4.1% during three months) [32]. Although the mortality rate was lower than our study, the patients had a minor stroke [32].

In the present study, we did not compare our subjects with the group who did not receive thrombolytic therapy, but the results of comparing the two groups were different in previous studies. In Huisa et al. study on patients with minor stroke, there was no difference in mortality rate between the group with and without r-TPA treatment [32]. In a meta-analysis by the IST-3 collaborative group on all types of strokes with TPA treatment indication, the difference was evident, and the mortality rate was higher in the TPA recipient group [31]. Nevertheless, the mortality rate was lower in the study mentioned above than that in Sari Aslani's [30] and our studies.

Another finding of the present study was that ICH occurred in 40% of those who expired and in 4.47% of the survived, and the difference was significant. Thus, a complicated ischemic stroke with ICH (resulting from r-TPA administration) increases the risk of mortality.

Therefore, changes in the case selection criteria and injection methods, injection dose, and injection time result in better treatment with TPA. Even though the selection of cases is according to the 2018 AHA/ASA stroke early management guidelines [33], the higher mortality in the Iranian studies made us adjust the dose and contraindications to some extent for the Iranian population.

According to the results, the Mean±SD of the total NIHSS score of participants significantly decreased after receiving r-TPA, and it was consistent with the results of Aslani et al. research (admission score: 11.69 and discharge score: 6.35) [30], Dong et al. (admission score: 10.54 and discharge score: 5.18) [34] and Tosta et al. (admission score: 10.39 and discharge score: 5.94) [35], indicating the influential role of using TPA in reducing the NIHSS score. Carneiro et al. examined the treatment results in 13 patients of ischemic stroke with COVID-19 treated with TPA. They found that majority of the patients (61.5%) improved in follow-up. The mean NIHSS score was 14.5 (range:3-26) at the time of admission, and the mean NIHSS score was 7.5 (0-25) in the last follow-up (2 to 3 days later) [28]. In Mehta et al. study in the

US on 97 patients, 67% of patients receiving r-TPA had an acceptable improvement in the 3-month follow-up, and 32% of patients deteriorated (by measuring NIHSS) [25]. Khatri et al. investigated treatment outcomes in patients with ischemic stroke treated with r-TPA. Among 58 participants, the results of their study indicated significantly higher positive treatment outcomes (using the NIHSS) in patients treated with r-TPA than the group that did not receive thrombolytic therapy [36]. Greisenegger et al. conducted a study in Spain on 890 participants measuring NIHSS and modified Rankin Scale (mRS) scores. They found that the positive therapeutic outcomes were significantly higher in patients treated with r-TPA than in the group that did not receive thrombolytic therapy [37]. In another study in Spain, Urra et al. examined 58 participants and found that the frequency of positive therapeutic outcomes (based on NIHSS score) in patients treated with r-TPA was significantly higher than that in the group without thrombolytic therapy [38]. Huisa et al. studied 113 participants and found no statistically significant difference between positive treatment outcomes (using NIHSS and mRS scores and Barthel index) in patients treated with r-TPA and the group that did not receive thrombolytic therapy. After 90 days, 57.6% of patients in the TPA group and 68.9% of patients in the untreated group had a mRS score of 0 to 1. A Barthel index score of 95 to 100 was achieved in 75% of the patients in the IV TPA group versus 78.9% in the untreated group. In their study, the patients had a minor stroke [32] indicating that the treatment of minor stroke cases with r-TPA did not make much difference in outcome and it might not be necessary to use it.

The present study results indicated no statistically significant relationship between hypertension, diabetes mellitus, hyperlipidemia, and history of CVA with consequences and complications of r-TPA prescription. Furthermore, there was no significant correlation between changes of NIHSS with age, blood glucose level, platelet level, INR at admission, and the latency time to receive r-TPA. Our results were similar to the results of a study by Sari Aslani et al. Their study was conducted on 217 patients treated for venous thrombolytic due to stroke, and the patients were followed up for three months. In the end, there was no significant relationship between patients' 3-month disability with sex, age, the latency time of onset of symptoms and receiving r-TPA, and vital signs at admission. However, the patients with a blood glucose of below 144 had better 3-month outcomes [30].

The secondary analysis after completion of the r-TPA stroke trial of the national institute of neurological disorders and stroke failed to identify the independent factors that alter the response to alteplase treatment [28]. However, some studies identified the relationship between treatment outcome and some factors. Albers et al. found a significant relationship between NIHSS score and a history of hypertension [23]. Demchuk et al. studied 1205 patients from the United States, Canada, and Germany, who received intravenous alteplase due to ischemic stroke. They found that mild initial severity of the stroke, absence of a previous history of diabetes mellitus, normal CT scan, normal blood glucose level, and normal blood pressure before starting treatment were independent predictors of a good prognosis [39]. Tseng et al. found that risk factors associated with adverse outcomes were female gender, older age, higher stroke severity index, low mean corpuscular hemoglobin concentration, low platelet count, and anemia [26]. In the Mehta et al. study, the severity of symptoms at admission, blood glucose at admission, age, and type of stroke affected the patients' outcomes [25]. Dae-Hyum Kim et al. studied 121 patients with mild stroke who received intravenous r-TPA in South Korea. They found that higher NIHSS score at admission, diabetes mellitus, and the infarction of deep middle cerebral artery were the predictors of adverse outcome for the patients, and the infarction of deep middle cerebral artery was independently associated with regression of neurological symptoms [40]. Another study by Chen et al. indicated that in addition to the time of starting treatment, the severity of the stroke and stroke subgroup could affect the benefits of r-TPA treatment [20]. In the present study, we examined most of the underlying diseases and did not examine all the parameters mentioned in other studies, but it is better to consider the influential factors in these studies in our practice.

Fraticelli et al. followed up stroke patients for three months and found that the female gender was associated with the worst functional outcomes [24]. Another study by Betts K.A. indicated that patients treated with r-TPA experienced longer survival, delays in hospital readmission, and a shorter period to get independence [41].

The results indicated that among the complications (13.7%), ICH was the most common complication (91.7% of complications), affecting 12.6% of participants. Also, as mentioned above, it has a higher incidence among those who expired rather than survived. Hematuria was the only other complication that occurred in one person. There was no statistically significant correlation between risk factors such as diabetes mellitus, a history of hypertension, hyperlipidemia, and a history of CVA with complications. In Carneiro et al. study, there was no case of intracerebral or systemic hemorrhage after prescription of r-TPA [28], but their study was conducted

on only 13 stroke patients. In Urra et al. study, the rate of ICH was equal to 6.7% (versus 2.7% in non-recipients) [38]. Albers et al. found that the ICH rate was 11.5% (3.3% symptomatic and 8.2% asymptomatic) [23]. In a meta-analysis and systematic review study by Wardlaw et al., who examined 12 studies, 272 cases of symptomatic ICH was seen among 3548 patients (7.7%) versus 63 cases among 4363 patients (1.4%) who did not receive TPA (OR=3.72 [2.98-4.64] P<0.0001) [15]. Wang et al. examined 57 consecutive patients with TPA from June 1996 to December 1998. Their results showed that the ICH rate was 9%, and 5% of cases were symptomatic [42]. In IST-3 collaborative group study, fatal or nonfatal symptomatic ICH within 7 days occurred in 7% of patients in the r-TPA group versus 1% in the control group (adjusted OR: 6.94; 95%CI: 4.07–11.8) [31]. It seems that the rate of ICH in the present study was somewhat larger than that in similar studies.

As the outcome of patients of the present study and another Iranian study by Sari Aslani et al. [30] was similar, and complications were more than the other studies, some modifications might be made in the selection of cases, the prescription dose, method of injection, and injection time conditions. In confirmation of this statement, one trial has suggested that using a lower dose of TPA (0.6 mg/kg) had a similar effect to the standard dose in a small sample size (in comparison with other similar studies) [43]. Also, a short follow-up duration was one of the limitations of that study.

Conclusion

The research results indicated that the participants' mortality rate was 23%. Also, 13.7% of patients developed complications, and ICH was the most common complication (12.6%). It has a higher incidence among those who expired rather than those who survived. NIHSS score of participants had a significant decrease after receiving r-TPA, indicating the effective and positive role of r-TPA prescription. However, there was no correlation between risk factors such as diabetes mellitus, hypertension, hyperlipidemia, and history of CVA with complications and outcomes. Therefore, none of the underlying factors of the patients might determine the prognosis of the results. Without considering them, except for cases with contraindications for use, this drug can be used to treat patients with stroke. Our mortality and ICH rates were slightly higher than studies in other centers. However, they can be decreased if some measures are taken for selecting cases, method of injection, the dose used, and the conditions during the injection. For example, we can control the blood pressure at a lower level, inject r-TPA in less time after the onset of symptoms, and perform magnetic resonance imaging with a diffusion-weighted magnetic resonance imaging sequence. Thus, better results of treatment with TPA might be achieved. Although the selection of cases is according to the 2018 AHA/ASA stroke early management guidelines, the higher mortality rate in Iranian studies encouraged us to adjust the dose and contraindications to some extent for the Iranian population. Albeit, the assessment of these changes requires further studies, especially in larger sample sizes and in other centers of Iran with longer follow-up periods and a control group.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1399.235). All study procedures were done in compliance with the ethical guidelines of the Declaration of Helsinki, 2013.

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Authors' contributions

All the authors contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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