



ORIGINAL ARTICLE

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## The effect of intravenous thrombolytic and intraarterial interventional procedures on acute stroke: First-year clinical experience of a stroke center in eastern anatolia

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### Abstract

Treating acute stroke in the early period can lead to reperfusion and minimize the loss of neurological function. In this study, our aim is to analyze the prognosis of our patients who underwent intravenous thrombolytic and/or mechanical interventional treatment in the last one year in our newly opened stroke center and evaluate our clinical experience. A total of 166 patients with a mean age of  $68.7 \pm 11.3$  who underwent intravenous r-tPA  $\pm$  mechanical thrombectomy in our stroke center were included in the study. The mean time from symptom-to-door was  $138.6 \pm 48.3$  min, and the mean NIHSS score on admission was  $10.9 \pm 4.1$ . Intravenous r-tPA was preferred for treatment in 59.6% (99) patients. The mortality rate was 25.3% (42) for all patients. The mortality rate was 15.1% (15/99) for patients receiving intravenous r-tPA, and based on this finding, the mortality risk was found to be significantly higher in patients who did not receive intravenous r-tPA ( $p < 0.001$ ). The mortality rate was 40% (6/15) for patients undergoing only mechanical thrombectomy ( $p: 0.145$ ). The mRS score of the patients who received intravenous r-tPA was 3.18 in the first month, whereas the score of the patients who did not receive intravenous r-tPA was 3.74 ( $p: 0.010$ ). As a result, mortality and sequelae rates have been significantly reduced with the use of thrombolytic therapy and interventional neurovascular procedures. Although our center is newly opened, it shows promise for the upcoming years.

**Keywords:** Stroke, thrombectomy, thrombolysis, cerebrovascular

### Introduction

Acute stroke is one of the leading causes of mortality and physical disability worldwide [1]. Early intervention in patients with stroke symptoms is very important. The aim of the treatment is to prevent permanent damage by arterial revascularization of the ischemic tissue, thereby preventing the formation of the ischemic penumbra. Approximately two million neurons are lost every minute in the area supplied by the occluded artery as long as the occlusion persists, and neurons comparable to 26 years of aging are lost after ten h [2]. Treatments that will provide recanalization are required to save the ischemic penumbra after stroke and restore perfusion [3]. Intravenous thrombolysis is an effective treatment that dissolves thrombus or embolism, which results in acute ischemic stroke, and restores blood circulation [4].

In Europe, the use of intravenous thrombolytic therapy [recombinant tissue plasminogen activator (r-tPA)] has been approved and continues to be practiced since 2002 [5]. Since 2015, therapies

combining endovascular treatment with intravenous interventions have been introduced in clinical practice in comprehensive stroke centers. Full recovery is observed in 1 of 4.5 patients treated in the first 90 min (intravenous r-tPA  $\pm$  mechanical thrombectomy), 1 of 9 patients treated within 90–180 min, and 1 of 14 patients treated within 180–270 min [6].

Our aim is to analyze the prognosis of our patients who underwent intravenous thrombolytic and/or mechanical interventional treatment in our newly opened stroke center within an approximately 1-year period based on the mRS scores observed on admission and in the first month and NIHSS scores observed on admission and at 24 h and evaluate our clinical experience. In addition, although we have little clinical experience in our center where we have just started providing interventional treatment, we aim to increase our experience in the coming days by analyzing the relationship between endovascular treatment initiation and clinical improvement.

### Materials and Methods

This study was carried out in accordance to the principles of the World Medical Association's Declaration of Helsinki and after obtaining approval of the Malatya Clinical Research Ethics Committee (approval number 2020/166). Our study was a single-

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center study, and it included 166 patients meeting the inclusion criteria, having a confirmed diagnosis of acute ischemic stroke based on clinical and radiological investigation, and those who were followed up in our stroke center after undergoing intravenous recombinant tissue plasminogen activator (r-tPA) ± mechanical thrombectomy between December 1, 2018, and February 1, 2020. The patients were reviewed retrospectively using electronic medical records. Patients older than 18 years of age were included in the study. Selection of eligible patients, treatment indications, and contraindications and treatment management were carried out according to the 2018 American Stroke Association guidelines [6].

Patient information was obtained from the hospital's online database (Nucleus® and Akgün® Hospital Information Management Systems) and patient observation files. The data were scanned separately by two researchers and evaluated. Demographic data of patients, such as age, gender, history, and clinical data, such as symptom-to-door time, symptom-to-needle time, modified Rankin scale (mRS) scores on admission and in the first month, NIHSS (National Institutes Of Health Stroke Scale) scores at 1 and 24 h, and Alberta stroke program early CT score were analyzed. Furthermore, the effects of clinical data on mortality and treatment options were analyzed. Patients with a clinical NIHSS score of >4 were included in the study. Patients presenting to the emergency department within the first 270 min from the onset of symptoms were included in the study.

For thrombolysis, the treatment protocol devised for the study patients was—intravenous alteplase (ACTILYSE® vials) administration at a dose of 0.9 mg/kg (maximum 90 mg), 10% of the total dose being administered as a bolus and the remaining intravenously over 60 min.

A digital subtraction angiography device (Siemens®) was used for endovascular treatment. For the diagnosis of the lesion, a 7F sheath was introduced into the right femoral artery and a 5F hydrophilic diagnostic catheter (Cordis®) and 0.035 hydrophilic guide wire (Aquatrack®) were used. For endovascular treatment, a 6F guiding catheter (Destination®) was placed proximal to the internal carotid artery (ICA). A 5F distal access catheter and 0.014 microguide wire (Synco®) were inserted into the cavernous segment of the ICA. A microcatheter was used to pass the thrombus (Rebar® 27). A stent retriever (Solitaire Platinum® 6/40) was deployed on the lesion through a microcatheter, and retraction and aspiration were performed. During the procedure, 200 ml of contrast material and 5,000 IU heparin were used intravenously, and the patients were sedated by the anesthesiologist.

The study data were analyzed using the SPSS package program for Windows, Version 20.0. Bivariate correlation (Pearson's *r* and Spearman's correlation tests) was used to evaluate the correlation between data. The chi-square test was used to compare categorical data. The study data were expressed as mean, standard deviation, number, and percentage. Firstly, the groups were analyzed in terms of their conformity to the normal distribution. The Shapiro–Wilk test and skewness and kurtosis values were used to analyze whether the data were normally distributed. Analysis of variance was used to evaluate repeated measures, and the Mann–Whitney U test was used for the analysis of independent data without normal distribution. A *p*-value of <0.05 was considered statistically significant.

## Results

A total of 166 patients with a mean age of 68.7±11.3 who underwent intravenous r-tPA ± mechanical thrombectomy in our stroke center were included in the study. Hypertension was the most common risk factor that was detected in 81.3% of the patients followed by atrial fibrillation and other cardiac causes. The rate of patients with recurrent ischemic cerebrovascular accident was 13.3%. The rate of individuals with ≥50% occlusion in the ICA on the symptomatic side was 12.7% (Table 1).

The symptom-to-door time was 138.6±48.3 min. The mean NIHSS score on admission was 10.9±4.1. The number of patients with symptom-to-door and symptom-to-needle times of <2 h was 67 (40.4%) and 32 (19.3%), respectively. Intravenous r-tPA was preferred for treatment in 59.6% (99) of the patients, and hemorrhagic transformation occurred in 11 patients receiving intravenous r-tPA (Table 2).

NIHSS scores observed at 1 and 24 h was not significantly different between patients with a symptom-to-door time of <2 h and those with a symptom-to-door time of >2 h. A significant improvement was observed at 24 h in the NIHSS scores of patients receiving intravenous r-tPA and those undergoing intravenous r-tPA ± mechanical thrombectomy (*p*<0.001). The mortality rate was 25.3% (42) for all patients. The mortality rate was 15.1% (15/99) for patients receiving intravenous r-tPA, and on the basis of this finding, the mortality risk was found to be significantly higher for patients who did not receive intravenous r-tPA (*p*<0.001). The mortality rate was 40% (6/15) for patients undergoing only mechanical thrombectomy (*p*: 0.145). Mortality was observed in 13 out of 67 patients with a symptom-to-door time of <2 h, and no difference was found in mortality for those with a symptom-to-door time of 121–270 min (*p*:0.104). When we look at the relationship between symptom-to-needle time and mortality, there was no significant relationship between the two groups (*p*:0.239). We evaluated the correlation between treatment options and clinical improvement. The mRS score of the patients who received intravenous r-tPA was 3.18 in the first month, whereas the score of the patients who did not receive intravenous r-tPA was 3.74 (*p*: 0.010). The mRS score in the first month did not significantly differ between patients who underwent only mechanical thrombectomy and those who did not undergo the procedure (*p*: 0.372) (Table 3).

**Table 1.** General characteristics and risk factors

<b>Age (minimum–maximum)</b>	68.70±11.3 (23-88)
<b>Gender: Female/Male (%)</b>	92(55.4)/74 (44.6)
<b>Length of stay (days)</b>	8.1 (5.5)
<b>Risk factors [n (%)]</b>	
• Hypertension	135 (81.3)
• Atrial fibrillation	48 (28.9)
• Other cardiac diseases	59 (35.5)
• Recurrent CVD	22 (13.3)
• Diabetes mellitus	71 (42.8)
• Carotid stenosis	21 (12.7)

**Table 2.** Time until treatment initiation, clinical scores, and treatment options

<b>Symptom-to-door</b>	Time (min)	138.6±48.3
	0-120 min [n (%)]	67 (40.4)
	121-270 min [n (%)]	99 (59.6)
<b>Symptom-to-needle</b>	Time (min)	172.1±50.1
	0-120 min [n (%)]	32 (19.3)
	121-270 min [n (%)]	134 (80.7)
<b>NIHSS</b>	Arrival	10.9±4.1
	1 h	9.6±4.9
	24 h	9.2±5.1
<b>ASPECT</b>		7.28±1.6
<b>Treatment, n (%)</b>	Intravenous r-tPA	99 (59.6)
	MT	15 (9.0)
	Intravenous r-tPA + MT	52 (31.3)
<b>Hemorrhagic trans, n (%)</b>	Intravenous r-tPA,	11 (6.7)
	MT	4 (2.4)
	Intravenous r-tPA + MT	14(8.5)

**Table 3.** Effects of treatment method and initiation time on clinical scores and mortality

		Arrival NIHSS	P	24 hr NIHSS	P	Arrival m-RS	P	1 month m-RS	P	Mortality n (%)	P
<b>Symptom-to-door</b>	0-120 min	10.37±4.34	0.138	8.46±5.16	0.088	4.26±0.79	0.726	3.16±0.88	0.079	13(7.8)	0.104
	121-270 min	11.34±3.94		9.86±5.11		4.31±0.88		3.54±1.29		29(17.5)	
<b>Symptom-to-needle</b>	0-120 min	9.47±4.62	0.023	7.53±5.43	0.031	3.97±0.83	0.018	2.68±0.71	0.001	6(3.6)	0.239
	121-270 min	11.31±3.93		9.72±5.02		4.37±0.83		3.54±1.18		36(21.7)	
<b>Iv r-tPA</b>	Yes	9.92±4.24	0.000	8.11±5.22	0.000	4.00±0.91	0.000	3.18±1.12	0.010	15(9.0)	0.000
	No	12.48 ±3.44		11.06 ±4.62		4.71±0.48		3.74±1.13		27(16.3)	
<b>MT</b>	Yes	12.33 ±4.45	0.175	10.62 ±4.92	0.336	4.64±0.49	0.103	3.00±1.15	0.372	6(3.6)	0.145
	No	10.81 ± 4.08		9.17±5.18		4.26±0.86		3.40±1.15		36(21.7)	
<b>Iv r-tPA + MT</b>	Yes	12.52 ±3.15	0.001	11.17 ±4.56	0.001	4.73±0.49	0.000	3.89±1.09	0.001	21(12.7)	0.003
	No	10.24±4.32		8.41±5.21		4.08±0.90		3.16±1.12		21(12.7)	

Iv r-tPA: intravenous recombinant tissue plasminogen activator  
 MT: mechanical thrombectomy

## Discussion

Of all the cases of stroke, 80%–85% were classified as ischemic stroke cases and the remaining 10%–15% as hemorrhagic stroke cases [7]. Stroke centers are dedicated healthcare units where patients diagnosed with ischemic and hemorrhagic infarcts are followed up. Functional independence and clinical prognosis of patients can be demonstrated using mRS. It is a 7-point scale ranging from 0 (no symptoms) to 6 (death). A score of ≤2 indicates a favorable clinical outcome, i.e., functional independence [8]. In stroke centers, it is aimed to standardize the diagnostic and therapeutic methods to be employed in stroke patients and provide the most appropriate and effective treatment to patients without delay [9].

In a study by Gargano et al. involving 1,922 patients, 19% of the patients presented to the emergency department due to stroke within the first 2 h, whereas 22% patients presented between 2 and 6 h and 59% presented after 6 h [10]. In a study by Kıyan et al. involving 124 patients, it was seen that 20.5% of the patients were admitted to the hospital within the first 3 h from the onset of their complaints [11]. In a study by Soyudogru et al. involving 122 patients, 13.9% of the patients were admitted to the hospital within the first 3 h, 45.9% between 3 and 6 h, and 25.4% of the patients had a delayed admission to the hospital (after 24 h) [12]. In our study, 166 patients were included in the study, and 40.4% patients presented to the emergency department within the first 1 h.

In the National Institute of Neurological Disorders and Stroke study

conducted in 1995, which is the first study examining intravenous administration of r-tPA in ischemic stroke during a period between 1991 and 1994, favorable clinical outcomes were demonstrated in 624 patients who received intravenous r-tPA treatment within the first 3 h after the onset of symptoms. In European Cooperative Acute Stroke Study-III evaluating 821 patients between 2003 and 2007, the time until the administration of intravenous r-tPA was increased from 3 h to 4.5 h [13, 14].

Between 2010 and 2014, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands was conducted in the Netherlands [15]. In this study, patients undergoing mechanical thrombectomy within 6 h of symptom onset and patients receiving standard intravenous r-tPA were compared. In addition, 267 patients with acute ischemic stroke diagnosed with proximal artery occlusion received intravenous r-tPA and 233 received intraarterial thrombolytic therapy along with intravenous r-tPA therapy. As a result, the rate of patients with a mRS score of 0–2 was 32.6% in the first group receiving intraarterial therapy and 19.1% in the second group receiving intravenous r-tPA. The rate of intracranial hemorrhage was 7.7% in the first group and 6.4% in the second group, and the 30-day mortality was 18.4% and 18.9, respectively [15].

In the present study, the mRS score in the first month was  $3.00 \pm 1.15$  in patients undergoing only mechanical thrombectomy and  $3.40 \pm 1.15$  in those who did not undergo mechanical thrombectomy. This finding suggests that mechanical thrombectomy had no favorable effect on the mRS score in the first month ( $p: 0.372$ ). However, the other two treatment options had favorable effects on clinical improvement. The improvement in the mRS score in the first month was remarkable in patients undergoing intravenous r-tPA + mechanical thrombectomy. The mean mRS score in the first month was  $3.89 \pm 1.09$  in patients undergoing r-tPA + mechanical thrombectomy and  $3.16 \pm 1.12$  in those who did not undergo this procedure ( $p: 0.001$ ). The mortality rate for all patients was 25.3% ( $n: 42$ ). When we look at the mortality relationship between the treatment groups, mortality was observed in 6 out of 15 patients (40%) who underwent only mechanical thrombectomy. The mortality rate was 15.1% in those receiving intravenous r-tPA, which was determined as the least risky treatment option. It is a striking finding that the mortality rates in our center are particularly high in patients undergoing only mechanical thrombectomy. This can be explained by the limited number of patients undergoing interventional treatment due to the fact that our center has been recently opened and the relatively limited technical experience.

The IMS (Interventional management of stroke) I–II and RECANALISE studies comparing angiographic reperfusion outcomes reported a decrease in the success rate with increasing time between reperfusion and symptom onset. In IMS I–II studies, mechanical thrombectomy was performed in 117 out of 161 patients. Successful reperfusion was achieved in 54 cases. The mRS score was 0–2, and the clinical outcomes were favorable in 29 out of 54 patients in whom reperfusion was achieved. However, the results were associated with a 10% reduction in the probability of functional independence for each 30-min delay in starting the angiography procedure [16]. In our study, 13 patients presenting to the emergency department within the first 120 min of the event died, whereas 54 recovered. The mRS scores on

admission and in the first month were 3.97 and 2.68, respectively, in patients presenting to the emergency department within 120 min and undergoing mechanical thrombectomy and 4.37 and 3.54, respectively, in patients presenting to the emergency department after 120 min. Accordingly, the mean mRS scores were higher and clinical outcomes were poor in patients with delayed presentation to the emergency department. Of patients presenting to the emergency department within 120 min after the onset, 13 died and 54 recovered. The mean mRS scores on admission and in the first month were lower in patients presenting to the emergency department within 120 min and undergoing mechanical thrombectomy ( $p=0.01$ ) than in patients presenting to the emergency department after 120 min ( $p=0.00$ ). This shows that early presentation to the emergency department and intervention is associated with more favorable disease course.

In the IMS III study, when standard intravenous r-tPA was compared with intravenous r-tPA + mechanical thrombectomy, it was determined that the combined treatment did not show any superiority over monotherapy [17]. In our study, the mean mRS score in the first month was  $3.89 \pm 1.09$  in patients receiving combination therapy (intravenous r-tPA + mechanical thrombectomy), whereas in the monotherapy groups, the mean mRS score in the first month was  $3.18 \pm 1.12$  in patients receiving only intravenous r-tPA and  $3.00 \pm 1.15$  in those undergoing only mechanical thrombectomy. This finding is in line with those of the IMS III study.

In a prospective study, 1,488 patients undergoing endovascular treatment between 2014 and 2016 were analyzed. According to the data obtained, it was determined that the mortality rate increased as the time from the onset of symptoms to endovascular treatment initiation increased. Every 1-hour delay in access to endovascular therapy was associated with a 5.3% reduction in the functional independence scale score [18]. Similarly, in our study, the mean mRS score was  $3.97 \pm 0.83$  ( $p=0.018$ ) on admission and  $2.68 \pm 0.71$  ( $p=0.001$ ) in the first month in patients with a symptom-to-door time of 0–120 min, whereas the mean mRS score on admission and in the first month were  $4.37 \pm 0.83$  and  $3.54 \pm 1.18$ , respectively, in patients presenting to the emergency department after 120 min. Consistent with the literature, it was observed that the prognosis was more favorable in patients presenting to the emergency department within 120 min due to low mRS scores.

The endovascular treatment can be beneficial provided that it is initiated within 90 min from the start of intravenous r-tPA and within 2 h after the onset of stroke symptoms; however, it can lead to complications when these conditions are not met [17].

In the Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS EXP) study, treatments given to 362 patients within 4.5 h of symptom onset were divided as standard intravenous r-tPA treatment, which was administered to 181 patients, and mechanical thrombectomy or intraarterial tPA treatment, which was administered to 181 patients. Most of the patients receiving intraarterial therapy received intravenous r-tPA. There was no significant difference between the two treatments based on the mRS score on the third month. Symptomatic intracranial hemorrhage was observed at a rate of 6% in both groups [19]. In our study, the mRS score in patients receiving r-tPA was 4 on admission and 3.18 in the first month, whereas the mRS score in patients who did not receive r-tPA was 4.71 on admission and 3.74 in the first month.

The mRS score in patients undergoing mechanical thrombectomy was 4.64 on admission and 3 in the first month, whereas the mRS score in patients who did not undergo mechanical thrombectomy was 4.26 on admission and 3.40 in the first month. The mRS score in patients receiving combination therapy (intravenous r-tPA + mechanical thrombectomy) was 4.73 on admission and 3.89 in the first month. In other words, the mRS scores of the patients receiving combination therapy were higher than that of the others and were associated with an unfavorable clinical prognosis.

## Conclusion

In conclusion, time is an extremely important factor in stroke treatment. Therefore, the initial clinical evaluation and follow-up of patients with a prediagnosis of stroke are of great importance for the effectiveness of revascularization treatments. Intravenous thrombolysis and mechanical thrombectomy, which are the main treatment methods employed for this purpose, have time-dependent efficacy. Since our clinic has been opened recently, it has limited experience, but it shows promise for the upcoming years.

## Conflict of interests

*The authors declare that they have no competing interests.*

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## Ethical approval

*Ethical approval for this study was obtained from Malatya Clinical Research (approval number: 2020/118) and the principles of the Helsinki Declaration were followed.*

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