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Efficacy of Intra-Arterial vs. Intravenous tPA Monotherapy in Acute Ischemic Stroke Treatment

Akut İskemik İnme Tedavisinde Sadece İntra-Arteriyel tPA ile Sadece İntravenöz tPA'nın Karşılaştırılması

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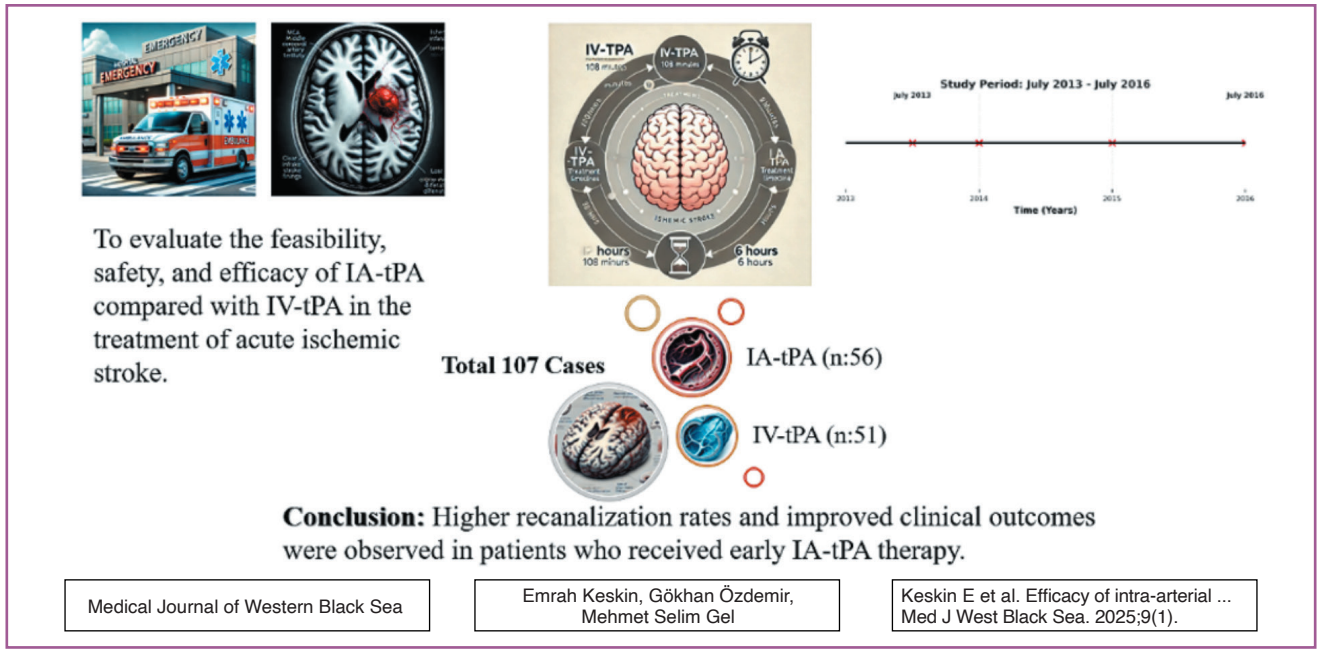
GRAPHICAL ABSTRACT



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ABSTRACT

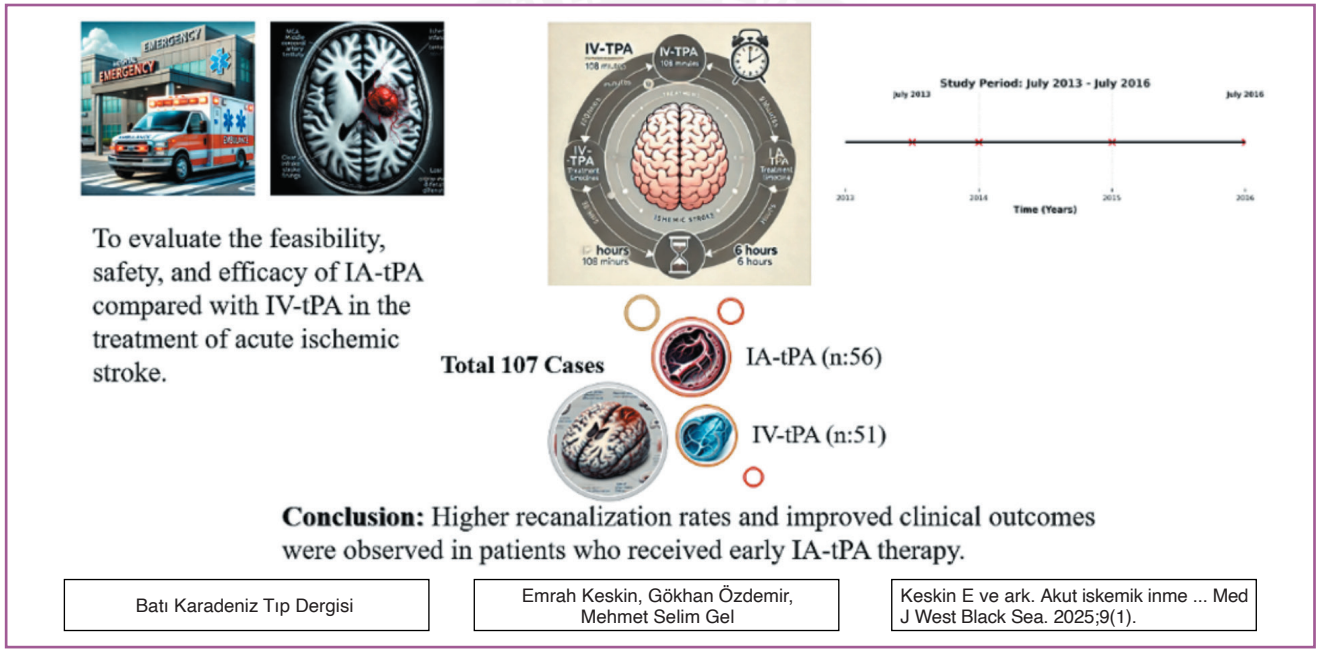
Aim: The method and timing of administration of tissue plasminogen activator (tPA) in the treatment of acute ischemic stroke (AIS) remain unclear. In our study, we aimed to compare the effectiveness of intra-arterial (IA)-tPA compared to intra-venous (IV)-tPA in AIS.

Material and Methods: Patients with AIS received IV-tPA within one hundred and eight minutes or IA-tPA within the first six hours. Before both treatments, their conditions were evaluated and treatments were performed. AIS patients were divided into those receiving IV alteplase (maximum 0.90 mg/kg) and those receiving IA alteplase (maximum 0.30 mg/kg). Demographic characteristics, systemic diseases and clinical outcomes were evaluated in both groups.

Results: It was observed that the clinical findings of the patients in the IA group were worse at the time of admission, but were better than those in the IV group after the procedure. While the ICH rate was similar in both groups (p>0.817); the recanalization rate was higher in the IA group compared to the IV group (p<0.001). Patients receiving IA treatment with alteplase doses of 20 mg or less had better clinical improvement (p = 0.020). In the IA group, the relationship between recanalization rate and the time of the onset of early treatment was statistically significant (p = 0.007).

Conclusion: According to the findings of our study, IA administration of tPA in the treatment of AIS is a more effective and applicable treatment option than IV administration. In addition, since higher recanalization rates and better clinical outcomes are observed in patients who receive IA-tPA treatment in the early period, more effective results can be obtained, especially in patients with large vessel occlusion.

GRAFİKSEL ÖZET



ÖZ

Amaç: Akut iskemik inme (Aİİ) tedavisinde doku plazminojen aktivatörünün (tPA) uygulanma yöntemi ve zamanlaması hala belirsizliğini korumaktadır. Çalışmamızda, Aİİ'de intra-arteriyel (İA)-tPA'nın intra-venöz (İV)-tPA ile etkinliğini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Aİİ'li hastalara yüz sekiz dakika içinde İV-tPA veya ilk altı saat içinde İA-tPA verildi. Her iki tedaviden önce durumları değerlendirildi ve tedaviler uygulandı. Aİİ hastaları İV alteplaz (maksimum 0,90 mg/kg) alanlar ve İA alteplaz (maksimum 0,30 mg/kg) alanlar olarak ayrıldı. Her iki grupta da demografik özellikler, sistemik hastalıklar ve klinik sonuçlar değerlendirildi.

Bulgular: İA grubunun çalışmanın başlangıç noktasında İV grubuna göre daha yüksek Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) ve modifiye Rankin skorları (mRS) olmasına rağmen, iyi klinik sonuçlar İA grubunda daha iyiydi. Her iki gruptaki intrakranial kanama oranı benzer iken (p >0,817); rekanalizasyon oranı İA grubunda İV gruba kıyasla daha yüksekti (p<0,001). İA grubunda, rekanalizasyon oranı ile erken tedavinin başlama zamanı arasındaki ilişki istatistiksel olarak anlamlıydı (p = 0,007).

Sonuç: Çalışmamızın bulgularına göre Aİİ tedavisinde tPA'nın İA uygulanması, İV uygulanmasına göre daha etkili ve uygulanabilir bir tedavi seçeneğidir. Ayrıca erken dönemde İA-tPA tedavisi uygulanan hastalarda daha yüksek rekanalizasyon oranları ve daha iyi klinik sonuçlar gözlendiğinden, özellikle büyük damar tıkanıklığı olan hastalarda daha etkili sonuçlar elde edilebilir.

Anahtar Sözcükler: İntra-arteriyel, intra-venöz, tPA, akut, iskemik İnme

INTRODUCTION

The first hours are critical in the treatment of acute ischemic stroke (AIS). Many studies show that tissue plasminogen activator (tPA) administered up to 4.5 hours after the onset of the first symptoms in AIS can improve clinical outcomes (1-3). On the other hand, IV alteplase is considerably less successful at restoring blood flow in the proximal segments of the principal intracranial arteries (middle cerebral artery (MCA), basilar artery) (4). The additional impact of intra-arterial (IA) tPA may vary depending on whether the initial treatment is IV-tPA or a conventional therapy. Given the treatment's extended time window, a localized IA thrombolytic infusion could prove beneficial for stroke patients presenting later. In patients who cannot receive IV tPA, IA tPA is recommended for strokes caused by blockage of a large vessel such as the MCA artery. The time required to administer IA tPA may be the first six hours from the onset of symptoms (5-7).

Intra-arterial thrombolysis (IAT) provides several benefits compared to IV thrombolysis (IVT). For instance, angiographic planning enables a tailored treatment strategy; targeted injections deliver a high local concentration of the drug while minimizing the overall dose, and mechanical devices can either accelerate recanalization or enable it when drugs alone are insufficient (8). In contrast to IVT, IA treatment is a lengthier and more invasive process. It also relies on costly technologies that are typically accessible only at specialized centers equipped with neuro-interventional teams (9). Successful vessel recanalization is linked to superior clinical outcomes (10). Although overall mortality rates are the same, the clinical consequences of intracranial hemorrhage (ICH) are higher. (11).

This study compared the clinical outcomes of both treatment approaches while controlling for factors like age, chronic conditions, and smoking habits. Ultimately, we aimed to evaluate the superiority of using only IA-tPA compared to using only IV-tPA in treating AIS.

MATERIALS and METHODS

Study Design

The main objective of this study was to determine if stroke patients undergoing IAT in the experimental group were more likely to achieve functional independence at 90 days than those receiving IVT in the control group. Patients with a modified Rankin scale (mRS) score of 0 at the third month of treatment were considered cured. The study also aimed to compare both groups regarding neurological impairment—assessed by National Institutes of Health Stroke Scale [NIHSS] scores on days 0, 1, and 7—and treatment safety, evaluated through the rates of symptomatic ICH, fatal and nonfatal strokes, overall mortality, and any neurological decline within the first week. In addition, patients' ages, chronic diseases (diabetes mellitus (DM), hypertension (HT), atrial fibrillation (AF), hypercholesterolemia), current cigarette smoking, survival times were compared between the two groups by examining their files.

Study Population

All patients diagnosed with AIS based on computed tomography (CT) and/or magnetic resonance imaging (MRI) findings who were consecutively admitted to our stroke center were enrolled in this study. The patients were 16 years of age or older (there was no upper age limit in the IA-tPA group, but the age limit was 80 years old in the IV-tPA group) and had AIS caused by an intracranial occlusion. The patients were recruited from July 2013 through July 2016. The included study randomized 107 patients (IA-tPA n =56, IV-tPA n = 51). Patients were admitted to hospitals by air or road, and all patients received IA-tPA within a six-hour window and IV-tPA within a 4.5-hour window, per NINDS criteria. All patients or their family members consented to thrombolytic treatment. Patients presenting with ICH or significant cerebral edema detected on CT scans were excluded from the study. Additional exclusion criteria included prior significant disability (mRS >2), severe comorbid conditions, and contraindications for thrombolytic therapy (Table 1) (12). The baseline assessment involved neurological and physical examinations, stroke severity scoring via the NIHSS and mRS scales, routine blood tests, electrocardiography and CT/MRI. Before the intervention, digital subtraction angiography (DSA) was conducted on candidates for IA-tPA to evaluate their vascular condition.

Following thrombolytic therapy, all patients had a follow-up CT scan within 24 hours. On the seventh day, additional imaging studies, including MRI, magnetic resonance angiography, and duplex ultrasonography, were performed to evaluate vascular and neurological recovery.

IV-tPA administration involved alteplase (50 mg, Boehringer Ingelheim, Rhein, Germany) at a dose of 0.9 mg/kg (maximum 90 mg), with an initial 10% bolus followed by a continuous infusion over 60 minutes. IA-tPA was delivered locally with a maximum of 30 mg in the carotid system and 20 mg in the vertebrobasilar system. Patients in the IA group were treated within 45 minutes of arriving at the hospital, and DSA was used post-procedure to assess recanalization success. IV heparin (25000 IU/ml, Pharmada, Istanbul, Türkiye) was initiated with a 3000-10000 U bolus during procedures in which IA-tPA was performed. General anesthesia was not administered (only two patients were given sedation). The IA-tPA patients were treated within 45 minutes (from the emergency to the intervention). Using a steerable microguidewire, an infusion microcatheter featuring a single distal opening was navigated into the thrombus's core. Sometimes the catheter may not be placed in the thrombus

Table 1. Major inclusion and exclusion criteria (12).

Inclusion criteria
- Sudden focal neurological deficit attributable to a stroke.
- Start within the first 4.5 hours for IV treatment; start within the first 6 hours for IA treatment
- Age between 16 and 80 years in IV-tPA (no upper age limit in IA-tPA).
CT/MRI exclusion criteria
- ICT except for small lesions
- Brain hemorrhage regardless of size
- Acute infarction or edema
Other exclusion criteria
- Poor level of consciousness at the time of first presentation (coma)
- Severe stroke as assessed clinically (eg, NIHSS score .25)
-Patients with rapid improvement in neurological status and minor symptoms
-Any major surgery or trauma within the last four weeks
- Baseline INR greater than 1.3, aPTT more than 1.5 times normal
- Platelet count less than 100 000 per cubic millimeter
- Blood glucose concentrations below 60 mg/dl or above 400 mg/dl
-Blood pressure ≥185 mm Hg systolic or ≥110 mm Hg diastolic on at least 3 consecutive measurements or uncontrolled hypertension that does not respond to treatment
- Situations in which the administration of thrombolytic drug is contraindicated

IV: İntra-venous, **IA:** intra-arterial, **CT:** computed tomography, **MRI:** Magnetic resonance imaging, **ICT:** intra-cranial tumor, **aPTT:** activated partial thromboplastin time, **INR:** international normalized ratio, **NIHSS:** National Institutes of Health Stroke Scale, **mRS:** modified Rankin Scale.

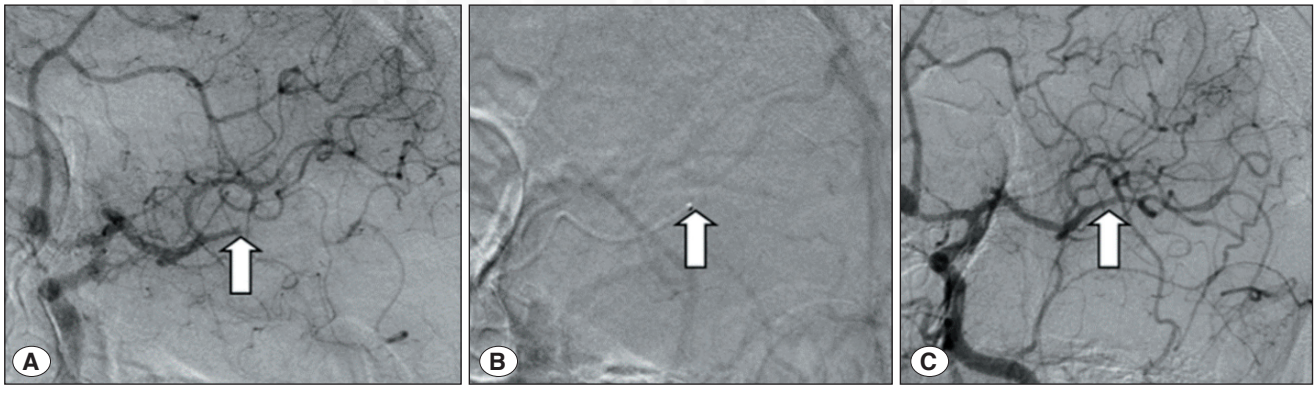


Figure 1: Obstruction is observed in the narrowing of the middle cerebral artery **(A)**, and after advancing the microcatheter **(B)** to the distal part of the obstruction, recanalization **(C)** was achieved by removing the clot with the help of aspiration and a retriever stent.

area. In this case, the catheter was parked as proximal to the thrombus as possible. At this stage, a superselective angiogram was performed to see the relationship between the catheter and the thrombus (Figure 1). This treatment procedure was performed in accordance with the European Stroke Organization guidelines (13).

All patients in both treatment groups were kept under observation in the stroke intensive care unit due to the importance of close monitoring of the process. In addition, control cranial CT scans were performed on the patients 24 hours after treatment. Antiplatelet therapy and low-dose subcutaneous heparin (25000 IU/5 ml, Pharmada, Istanbul, Türkiye) were started in all patients without bleeding on CT scan.

Patient records were scanned from the archives and risk factors were assessed. These were age, sex, HT, diabetes mellitus (DM), smoking status, hypercholesterolaemia, heart disease, AF (Table 2). We also examined patients already taking antiplatelets to determine the drugs' effects on ICH and the effectiveness of the treatment.

Statistical Methods

Statistical evaluation was performed using SPSS 18.0. The minimum and maximum values of the descriptive statistics, numbers, percentages of categorical variables, average of numeric variables, standard deviation, hydrangea, percentile 25 (Q1), and percentile 75 (Q3) were presented. The normal distribution of variables was examined using visual (histogram and probability graphics) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. The Mann-Whitney U Test was used in two independent group comparisons in which no normal distribution condition was provided for numerical variables. The Students'-test was performed when the normal distribution was provided. For independent multiple-group comparisons, an analysis of variance (ANOVA) was applied when the assumption of normal distribution was met, whereas the Kruskal-Wallis test was utilized when this assumption was not satisfied. In the post hoc analyses, the Mann-Whitney Test was performed using the Bonferroni correction. The chi-squared test was performed for binary and multiple comparisons of the categorical variables, the Fisher's Exact Test was performed for binary comparisons not provided by the chi-squared condition, and the Multi-Eyed Fisher's Extermination Test was used for multiple comparisons. For correlations that did not meet the normal distribution condition, Spearman's coefficient test statistic was used in relation to the numerical values. P values less than 0.05 were considered significant.

RESULTS

The patients' mRS scores on day 90 and NIHSS scores on days 1-7 were evaluated. The incidences of recanalization and ICH are presented in the Table 3. Although in the IA group had NIHSS and mRS scores that were higher than the scores of the IV group at the starting point, the improved results were better in the IA group. The recanalization rate was higher in the IA group (p<0.001, Table 3). The rate of ICH complications was similar in both groups. Although survival times were similar for both groups, they were better in the IA group (Figure 2).

In the IA group, the highest glucose values were found in those with ICH and in those who had recanalization (p = 0.018 and p = 0.004, respectively, Table 4). In the IA group, the improved NIHSS and mRS scores were correlated with low glucose values (p = 0.002 and p = 0.001, respectively, Table 4).

Table 2. Demographics and Vascular Risk Factors of Patients Treated With Intravenous and Intraarterial t-PA.

Characteristics	Intravenous (n=51)	Intra-arterial (n=56)	p
Mean age (Year±SD)	67.5±11.6	70.2±9.7	0.674
Hypertension, n (%)	37 (71.2)	41 (73.2)	0.291
Diabetes mellitus, n (%)	18 (34.6)	15 (26.8)	0.167
Hypercholesterolemia, n (%)	20 (38.5)	12 (21.4)	0.678
Current smokers, n (%)	10 (19.2)	15 (26.8)	0.259
Atrial fibrillation, n%	14 (26.9)	19 (33.9)	0.229
Heart disease, n (%)	26 (50.0)	41 (73.2)	0.141

SD: standard deviation, Mann Whitney Test

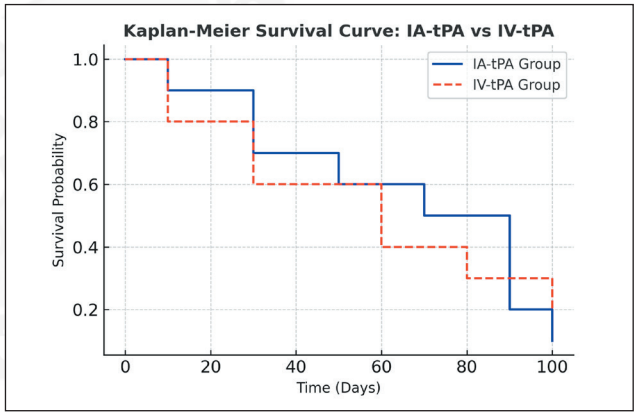


Figure 2: Results of Intra-arterial tPA and Intravenous tPA groups according to Kapla-Meier curve.

Table 3. Data on primary outcomes (scores on mRS at day 90 and NIHSS on days 1-7) and incidences of recanalization and ICH.

		IA Group (n=56)	IV Group (n=51)	p
NIHSS, (score±SD)	Start	17.2±5.62	15.86±2.27	0.106[A]
	Day one	14 (8.5-18)	12 (8-15)	0.049[C]
	Day seven	6 (4-12)	8 (6-12)	0.103[C]
mRS, (Q1-Q3)	Start	5 (4-5)	3 (3-4)	<0.001[C]
	Three months	1 (0-3)	2 (1-3)	0.051[C]
Recanalization	After treatment	41 (73.2%)	20 (39.2%)	<0.001[F]
Hemorrhage	After treatment	10 (17.9%)	10 (19.6%)	0.817[F]

ICH: intracranial hemorrhage, **IA:** intra-arterial, **IV:** intra-venosus, **NIHSS:** National Institutes of Health Stroke Scale, **mRS:** modified Rankin Scale, [A] Student T Test, [B] Anova, [C] Mann Whitney Test, [D] Kruskal Wallis Test, [E] Fisher's Extermination Test, [F] chi-square Test, [G] Multi-Eyed Fisher's Extermination Test, [H] Spearman Test

Table 4. In the IA treatment group; the relationship between hemorrhage, re-canalization, re-occlusion, NIHSS and mRS treatment results and glucose values.

IA Group Glucose Levels		Findings (n=56, Mean±SD)	p
Hemorrhage	Nope	124.78±24.98	0.018[A]
	Yes	146.2±25.93	
Re-canalization	Nope	145.07±18.2	0.004[A]
	Yes	122.59±26.32	
Post-recanalization	Nope	128.47±26.85	-*
	Yes	131±14	
Re-occlusion	Nope	128.35±24.69	0.819[A]
	Yes	131.2±42.97	
NIHSS Treatment Result	Nope	154.88±14.46	0.002[A]
	Yes	124.23±25.27	
mRS Treatment Result	Nope	154±13.77	0.001[A]
	Yes	123.74±25.31	

IA: intra-arterial, **SD:** standard deviation, **NIHSS:** National Institutes of Health Stroke Scale, **mRS:** modified Rankin Scale, [A] Student T Test, * Analysis could not be performed because the number of patients was not sufficient.

The patients in the IA treatment group who were given an alteplase dose of 20 mg or less had the most improved scores on the first day, at the end of the first week, and at the end of the third month of the study (p = 0.011, p = 0.020, and p = 0.007, respectively, Table 5). The decreased rate of ICH was found to be statistically significant in the IA patients who received alteplase doses of 20 mg or less (p = 0.032, Table 5).

DISCUSSION

Many studies have emphasized the importance of IA-thrombolysis for the treatment of AIS. This study showed that patients with AIS at various locations who received only IAT treatment had better functional outcomes than those who received only IVT treatment. In addition, this study showed that symptomatic ICH did not differ significantly between the treatment groups.

The IV administration of thrombolytic, or IVT, is one of the most well proven beneficial treatments for the emergency management of ischemic stroke (5). A local IA infusion of thrombolytic, or IAT, might also be beneficial for ischemic stroke patients. For patients who are not eligible for IVT, IAT is advised if initiated within six hours of a stroke onset caused by a blockage in the MCA (6, 7). Nonetheless, comparative studies evaluating the effectiveness of IAT versus IVT are currently limited.

Ciccone and Valvassori evaluated the clinical outcomes of 362 patients who were randomly treated with IVT or IAT.

Table 5. Relationship of alteplase dose with hemorrhage, re-canalization, re-occlusion, NIHSS and mRS treatment outcomes in the IA treatment group.

	IA-Alteplase Dosage Group		
	20 and under, (n=24)	20 and above, (n=32)	p
NIHSS	15.54±5.94	18.44±5.1	0.055[A]
NIHSS Treatment Result	11.5 (8-15.5)	17 (11-20.5)	0.011[B]
mRS Treatment Result	5 (3-8)	8 (4-18)	0.020[B]
	4 (3.5-5)	5 (4-5)	0.042[B]
Hemorrhage	23 (95.8)	24 (75)	
	23 (95.8)	23 (71.9)	0.032[C]
Re-canalization	1 (4.2)	9 (28.1)	
	22 (91.7)	29 (90.6)	1.000[C]
	2 (8.3)	3 (9.4)	
Post-recanalization	4 (16.7)	11 (34.4)	0.139[D]
	20 (83.3)	21 (65.6)	
Re-occlusion	22 (91.7)	31 (96.9)	-*
	2 (8.3)	1 (3.1)	

IA: intra-arterial; **NIHSS:** National Institutes of Health Stroke Scale; **mRS:** modified Rankin Scale, [A] Student T Test, [B] Mann Whitney Test, [C] Fisher's Extermination Test, [D] chi-square Test, * Analysis could not be performed because the number of patients was not sufficient.

The distribution of patients in both treatment groups was equal. In this study, they evaluated the disability-free survival rates of the patients. The 90-day survival rates were similar in both groups at 30%. In conclusion, they showed that IAT was not superior to standard therapy (14). Similarly, in the two randomized studies by Ducrocq et al. (15) and Ciccone et al. (9), a significant difference in favorable outcomes between IAT or IVT in conjunction with therapy was not found. In contrast, four studies with different numbers of subjects found more favorable outcomes with IAT than with IVT in patients with AIS (16-19).

In the present study, the IA group had more favorable NIHSS scores than the IV group. In this study, by the end of the three-month period, the IA group dropped from 17 points to 6 points, and the IV group dropped from 15 points to 8 points. In addition, over the three-month period, the mRS scores in the IA group dropped from 5 points to 1 point, and the IV group dropped 3 points to 2 points.

Saver et al. (20) emphasized the importance of administering speedy endovascular therapy with thrombectomy in patients who have achieved reperfusion. In the present study, such patients were taken into treatment with in 45 minutes (from the emergency department to groin puncture) in the IA-tPA group. This study showed that IA treatments applied

sooner after a stroke resulted in higher recanalization rates than IA treatments applied later after a stroke ($p<0.05$). However, there was no relationship between recanalization and treatment time in the IV group. The precise process by which bridging therapy enhances functional recovery has not yet been elucidated (21). Although the present study showed that the recanalization rates in the IA group were very high and were associated with improved NIHSS and mRS scores, these rates did not correlate with the improved scores. This study has highlighted that improved reperfusion was not a guarantee of clinical efficacy.

The primary objective in managing AIS is to restore circulation by reopening vessels that have been blocked (22). Recanalization can be attained by IV or IAT. Among patients receiving IVT, the overall rate of vessel reopening is around 46%; however, success drops significantly when the blockage involves a major artery (23-26). In the present study's IV group, the overall recanalization rate was 39.2%. Some studies have indicated that IAT tends to result in more effective vessel reopening compared to IVT (10, 18, 27). This study revealed that the IA group achieved significantly greater recanalization rates than the IV group ($p = 0.001$).

Recent studies on IAT have reported rates of ICH ranging from 0% to 33% (17, 28). Multiple studies have demonstrated that the incidence of symptomatic hemorrhage does not significantly differ between the treatment options (9, 14, 15). In this study, the IAT group experienced an ICH rate of 17.9%, yet no symptomatic hemorrhages were observed. The decreased rate of ICH was found to be statistically significantly in IA patients who received alteplase doses of 20 mg or less ($p = 0.032$). In addition, the patients who received the IA treatment and who were given alteplase doses of 20 mg or less had the most improved scores.

Different studies have observed differences between functional outcomes and risk factors in AIS patients. Ping Yu's research indicated that patients with better functional outcomes tended to be older, had a lower proportion of males, and showed a higher prevalence of AF, coronary heart disease, and DM. In addition to the different functional outcomes, clinical characteristics and smoking status of the patients also differed. These patients also had irregularities in terms of medication use (29). According to Tziomalos et al., factors such as older age, previous ischemic stroke and admission NIHSS score predicted poor outcomes at discharge as independent factors, while previous statin therapy was linked to more favorable outcomes (30-33). Individuals with stress-induced hyperglycemia experienced strokes that were more severe compared to those without this condition (32). In the IA group in the present study, the highest glucose value was found in those with the ICH and in those who had recanalization (respectively, $p = 0.018$ and $p = 0.004$, Table 4). In the IA group, the most improved NIHSS and mRS scores were correlated with lower glucose values (respectively, $p = 0.002$ and $p = 0.001$, Table 4).

This study's limitation was that the number of participants was restricted by the single-center nature of the study.

In conclusion, the use of immediate IAT as sole treatment for AIS patients is not only safer but also more effective than IVT alone in restoring blood flow, significantly reducing disability and increasing the percentage of individuals achieving functional independence three months after stroke.

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None.

Author Contributions

Conception, design, data collection, literature search, writting, approval: **Gökhan Özdemir,** Conception, design, literature search, writting, approval: **Gökhan Özdemir, Emrah Keskin,** Analysis and interpretation of data, writting, approval: **Emrah Keskin.** All co-authors have had the opportunity to review the final manuscript and have provided their permission to publish the manuscript.

Conflicts of Interest

There is no conflict of interest among the authors. Written consent for medical treatment was obtained from the families of cases under 18 years of age.

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Ethical Approval

The research was approved by the Research Ethics Committee at Selcuk University (certificate number 2018-5/80). Informed consent was obtained from all patients in the study.

Review Process

Extremey and externally peer-reviewed.

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