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Response to Systemic Thrombolysis in Different Ischemic Stroke Subtypes

Farklı İskemik İnme Alt Tiplerinde Sistemik Trombolitik Tedaviye Yanıt

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ABSTRACT

Background: Evidence based treatment of acute ischemic stroke is intravenous administration of fibrinolytic agents within the first 4.5 hours. The source of cerebral vessel occlusion may be important for recanalization. Current study is designed to find which ischemic stroke subtype benefit more from systemic thrombolysis.

Methods: Hospital records of patients who received only IV-tPA for acute ischemic stroke treatment are outlined retrospectively. Four etiologic subtypes, large arterial atherosclerosis, cardioembolism, lacunar infarct and other uncommon causes of stroke are included, patients with strokes due to undetermined source are excluded. The reduction of NIHSS score more than 7 or a final NIHSS score between 0-2 are defined as good response to thrombolytic treatment. The percentages of patients reaching to favourable outcome on day 1,7 and 90 are compared between different subtypes together with intracranial bleeding and mortality.

Results: Among 231 patient included, the good response rate was similar in strokes due to large arterial atherosclerosis and cardioembolism at day 1, 7 and 90 (28.8% versus 25% on day 1, 38.8% versus 35.8% on day 7 and 51.3% versus 50.8% on day 90). Lacunar infarcts did not respond to IV-tPA dramatically in the first week (25%), however improve better at the end of three months (75%). The rate of good responders did not significantly vary between different subtypes in all time points (OR: 0.784 at day 1, OR: 0.946 at day 7, OR: 1.219 day 90, P>.05). Low blood glucose level at the admission and low onset-to-time were significant determinant of early good response after adjustment (P<.05). Intracranial bleeding was higher in cardio embolic strokes..

Conclusion: The etiologic and physiopathologic mechanism of acute ischemic stroke does not affect the response to fibrinolytic treatment. Especially delays in infusion or high initial blood sugar levels lead to poor response. Withholding thrombolysis in patients with definite subtypes or the reverse have not been recommended.

Keywords: Ischemic stroke, etiologic subtype, thrombolysis.

ÖZ

Amaç: Akut iskemik inmenin kanıta dayalı tedavisi ilk 4.5 saatte intravenöz yolla fibrinolitik ilaçların verilmesidir. Serebral damar oklüzyonunun kaynağı rekanalizasyon için önemli olabilir. Bu çalışma hangi etiyolojik inme alt tipinin sistemik trombolizden daha fazla fayda gördüğünü göstermek için tasarlanmıştır.

Yöntemler: Akut iskemik inme tedavisi için tek başına IV-tPA tedavisi almış hastaların hastane kayıtları retrospektif olarak tarandı. Dört farklı inme alttipi, büyük damar aterosklerozu, kardiyoembolik inme, lakuner enfarktlar ve diğer nadir nedenlere bağlı inme hastaları çalışmaya dahil edildi, nedeni belirlenemeyen inmeler alınmadı. Trombolitik tedaviyle NIHSS skorunda 7 puan üzerinde düşüş veya 0-2 arasında NIHSS skoruna ulaşılması iyi yanıt olarak tanımlandı. Dört farklı inme alt grubunda 1,7 ve 90. günlerde iyi yanıt alınan hastaların oranları, intrakranial kanama ve mortalite oranları ile birlikte karşılaştırıldı.

Bulgular: Dahil edilen 231 hasta içinde, büyük damar aterosklerozu ve kardio embolizme bağlı olgulardaki iyi yanıt veren hasta oranı 1,7 ve 90. günlerde birbirine çok yakındı (1.günde %29'a karşılık %26, 7.günde %39'a karşılık %36, 90.günde %51'e karşılık %51, P>.05). Lakuner inmelerde ilk haftada dramatik yanıt gösteren hasta sayısı azdı (%75) ama 3.ayın sonunda düzelme (%75) daha fazla izlendi. Tüm zaman dilimlerinde, trombolitik tedaviye iyi yanıt veren hasta oranları açısından değişik inme alt tipleri arasında istatiksel anlamlı farklılık yoktu (1.günde OR: 0,784, 7.günde OR: 0,946, 90.günde OR: 1,219, P>.05). Düşük başvuru kan şekeri ve kısa semptom-iğne zamanı, ilk bir haftada iyi yanıt alınan hasta oranlarını çok değişkenli analizlerde anlamlı olarak artırıyordu (p<0.05). Kardiyo embolik inmelerde intrakranial kanama komplikasyonu daha sık görüldü (P<.05). Lakuner enfarktlarda ve diğer nadir nedenlere bağlı inmelerde mortalite izlenmedi.

Sonuç: Akut iskemik inmenin etiyolojik ve fizyopatolojik mekanizması fibrinolitik tedaviye yanıtı etkilememektedir. Tedaviye zayıf yanıtı belirleyen faktörler yüksek kan şekeri ve gecikmiş uygulamadır. Belirli inme alt tiplerinde trombolitik tedavinin askıya alınması veya endikasyon alanın spesifik inme alt tipleriyle sınırlanması önerilmez.

Anahtar Kelimeler: İskemik inme, etyolojik alt tip, tromboliz.

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INTRODUCTION

Intravenous (IV) infusion of recombinant human tissue type plasminogen activator (tPA) is the primary treatment of acute ischemic stroke within 4.5 hours of symptom onset.[1,2] It is indicated if there is no haemorrhage or a large early hypodensity on the initial computerised tomography regardless of the stroke aetiology.[3] In cases with major proximal vessel occlusion, mechanical thrombectomy is indicated in first 6 hours.[4] Thirty nine to fifty two percent of patients receiving systemic thrombolytic treatment become asymptomatic or non disabled at the end of 3 months, while 26-30% of the patients remains moderately to severely disabled and 7-17% of the patients die.[1,2]

Two main determinants of the efficacy of IV-tPA are the time to needle and the size of the penumbra. Admittance high blood sugar and high National Institutes of Health Stroke Scale (NIHSS) scores with large infarct and early infarct signs, presence of dense middle cerebral artery sign, atrial fibrillation and moderate to severe leukoaraiosis are predictors of poor response and higher risk of intracranial haemorrhage after systemic alteplase administration.[5,6]

Even if some data pull attention to relation between fibrinolysis and the composition and source of the clot, the etiologic cause of cerebral vessel occlusion is not considered as a criterion of choice or avoidance. White clots formed by platelets and lipid particles are supposed to be more resistant to systemic thrombolysis than red clots occupied by red blood cells and fibrin.[7]

The present literature considering the effect of IV-tPA and stroke subtype is controversial, there is no clear evidence showing that the use of intravenous thrombolysis in a specific stroke subtype will be harmful or unhelpful, nor is there sufficient data on which stroke subtype it will be most beneficial. The current study aims to demonstrate if there is difference in response to systemic thrombolytic treatment for acute stroke in the early and late stages among various ischemic stroke etiologic subtypes, together with a review of the present literature.

MATERIAL AND METHODS

The study was performed on the data of patients who admitted to a university hospital and received IV-tPA for the management of acute ischemic stroke, retrospectively between July 2007 and July 2024. The present hospital is a comprehensive stroke centre serving a population of about 2 million with another tertiary care hospital in the same region. Stroke mimics and patients who underwent endovascular treatment were excluded even if they received IV-tPA. Intravenous thrombolytic treatment decision for acute ischemic stroke was given according to the criteria described in National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study (ECASS) trials.[1,2] Electronic hospital records were outlined for patient age, gender, onset-to-needle time, admission NIHSS scores, blood glucose levels, blood pressure. The presence of atrial fibrillation, hypertension, diabetes, hyperlipidemia, coronary heart disease were recorded. Ischemic stroke etiologic subtype was determined according to Causative Classification System for Ischemic Stroke.[8] The subtype was retrospectively determined by considering clinical findings, the neuroimaging data including brain magnetic resonance (MR) basically diffusion weighted images, apparent diffusion coefficient maps or cranial computerized tomography (CT) scans, angiography of cranial vessels of neck and brain (MR, CT angiograms), cardiac investigations (electrocardiography, transthoracic echocardiography and 24 hours rhythm Holter monitoring or transesophageal echocardiography if needed), and blood tests for other rare causes of ischemic stroke. Patients with four definite ischemic stroke subtypes [large artery atherosclerosis (LAA), cardio embolism (CE), small vessel disease (SVD) and other uncommon causes of cerebral ischemia] were included, while strokes attributed to undetermined source were not included in the study. The flow chart of included patients is given in Figure 1. In this retrospective study, the requirement for informed consent was waived by the ethics committee due to the use of anonymized pre-existing data. The required Ethics Committee approval was obtained from the Clinical Research Ethics Committee of Ondokuz Mayıs University (Date: November 11, 2019; Decision No: OMU KAEK 2019/758). All procedures were performed in accordance with the ethical standards of the revised 2008 Declaration of Helsinki.

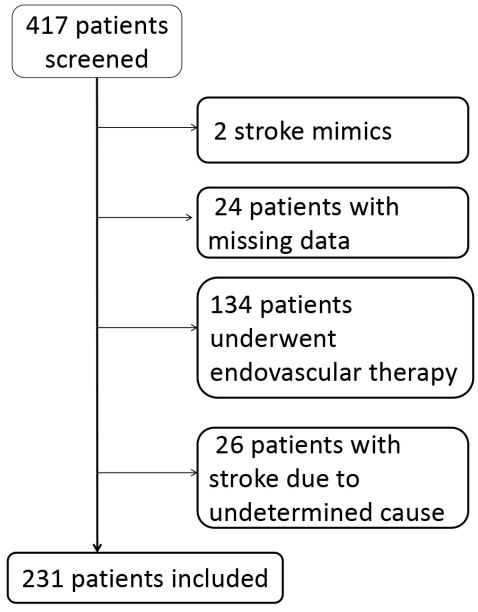

Figure 1: The flowchart diagram of the included and excluded patients.

Hospital records were checked for the determination of NIHSS scores on the 1st, 7th and 90th days. Mortality rates at the 90th day, and haemorrhagic complications due to IV-tPA treatment within the first 72 hours were recorded. The primary end point of the study was good response to systemic tPA administration on day 1, 7 and 90. Good response is described as NIHSS score reduction from the pre-treatment score more than 7,[2] or any NIHSS which reached to 0-2. That means, a patient with initial NIHSS score with 18 reaching to 10 or with

MAIN POINTS

- Intravenous thrombolysis is safe and effective in all ischemic stroke subtypes.
- Admission blood glucose level and onset-to-needle time were determinants of good response to IV-tPA within the first week.
- Patients younger than 70 have better outcome at the end of 3 months.

an initial score 4 reaching to 1 is accepted to gain good response. The secondary endpoints were modified Rankin scores at discharge and day 90 and any complications related with IV-tPA administration including allergic reactions, intracranial and extracranial haemorrhages within 72 hours and cumulative mortality at the end of 90 days.

The statistical analyses were performed by Statistical Package for the Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Kolmogorov Smirnov test was used to assess the normality of distribution. Bivariate analyzes were made by chi-square test for categorical variables, by Pearson or Spearman tests for continuous variables, and by Student t-tests or analysis of variance (ANOVA) for group-wise comparisons. Multivariate analyses for categorical dependent variables (1,7,90 day good response, 90-day intracranial haemorrhage and mortality) were applied by binary logistic regression analysis with an enter algorithm. A P value below .05 was considered to be statistically significant. Categorical variables are expressed as number and percentage (%) to gather with Odds Ratio (OR) and 95% confidence intervals (CI), and numerical variables as mean ± standard deviation (SD).

RESULTS

Total 231 patients were included. The mean age was 65±12. There were 136 males (59%) and 95 females (41%). Mean admission NIHSS score was 13±5. Mean symptom onset-to-needle time was 169±55 minutes (r:20-360 min) (Table 1). After re-evaluation of the clinical, laboratory and imaging findings, strokes were attributed to extracranial or intracranial large vessel atherothrombotic disease in 80 patients (34.6%), to cardio embolism in 120 patients (51.9%), to small vessel disease in 8 patients (3.5%) and to other rare definite causes of ischemic stroke in 23 (9.9%) patients. Mean admission NIHSS score was significantly higher in cardioembolic strokes against the lowest mean NIHSS score was observed in the SVD group (P<.01, Table 2).

In terms of primary endpoint, 60 of 231 patients (25.9%) had a reduction in NIHSS score more than 7 or any NIHSS score below 3, 24 hours after IV-tPA infusion. The good response after systemic thrombolytic treatment was observed in 87 patients (37.7%) at the end of 7 days, in 125 patients (54.1%) at the end of 90 days. At the end of first day, 23 patients in the LAA group (28.8%), 30 patients in CE group (25%), 6 of the others group (26.1%) and 1 of the SVD group (12.5%) had a reduction of NIHSS score more than 7. After 7 days, the best good response rate was present in patients with other rare causes of ischemic stroke (47.8%), while 38.8% of large vessel disease patients, 35.8% of cardioembolic patients and 25% of small vessel disease cases had a decrease in NIHSS scores more than 7 or a final NIHSS between 0 and 2. At the end of 90th day, the favourable outcome was present in 75% of patients with lacunar infarctions, 73.9% of strokes due to other causes, 51.3% of strokes due to intracranial or extracranial large vessel disease and 50.8% of cardio embolic strokes. The rate of good responders to IV-tPA (NIHSS reduction> 7 or NIHSS score 0-2) at the 1st, 7th and 90th days were significantly similar among different ischemic stroke subtypes (P>.05, Table 3).

At the end of 24 hours, the novel significant predictors of good response were found to be admission blood glucose level and onset-to-needle time (Table 1). Admission blood glucose levels and onset-to-needle time were significantly lower in good responders than non-responders at day 1, even in the multivariate analysis [P<.05, OR;95% CI:0.202 (0.057-0.716) for high blood glucose and OR;95% CI:0.463 (0.251-0.756) for onset-to-needle time]. Age was similar between good and poor responders on day 1 (good responders 67±13 versus poor responders 67±12, P>.05). Gender, admission mean arterial blood pressure, stroke subtype, accompanying atrial fibrillation, hypertension, diabetes, coronary heart disease and hyperlipidemia did not differ between good responders and non-responders (P>.05, Table 1 and 3).

Similarly, the good response to thrombolytic treatment at the end of first week was significantly more prevalent in patients with lower admission blood glucose and onset-to-needle time after adjustment [P<.01, OR;95% CI:0.220 (0.077-0.627) for admission blood glucose, OR;95% CI:0.492 (0.299-0.810), Table 1 and 3]. Additionally, the mean age was significantly lower in patients who gained a reduction of NIHSS scores more than 7 or who reached an NIHSS below 3 at the end of 7 days (good responders 63±13 versus poor responders 67±12 at day 7), and the reverse correlation persisted in multivariate analysis (P<.05, Table 1 and 3). There were no significant difference in the reduction of NIHSS scores among other research parameters at day 7 (P>.05, Table 1 and 3).

Table 1: Comparison of different parameters on response to thrombolytic treatment, complications and mortality.

		Day 1		Day 7		Day 90		Intracranial Hemorrhage		Mortality	
	All patients n=231 (Mean±SD)	Good responders n=60 (Mean±SD)	Non-responders n=171 (Mean±SD)	Good responders n=87 (Mean±SD)	Non-responders n=144 (Mean±SD)	Good responders n=125 (Mean±SD)	Non-responders n=106 (Mean±SD)	Present n=29 (Mean±SD)	Not n=202 (Mean±SD)	Present n=48 (Mean±SD)	Not n=183 (Mean±SD)
Age	65.68±12.24	66.81±12.58	67.28±12.11	62.68±12.85*	67.49±11.53*	62.21±11.92*	69.76±11.37*	67.1±10.42	65.47±12.49	72.25-9.77*	63.95-12.26*
Admission NIHSS	13.54±5.93	12.12±5.21	14.02±6.09	12.91±6.23	13.89±5.73	13.03±6.35	14.10±5.37	15.69±5.2*	13.21±5.97*	16.21-5.34*	12.82-5.89*
Admission MAP	104.06±45.13	99.89±31.99	106.28±19.78	101.68±29.23	106.38±19.48	101.49±24.46	108.18±22.33	117.39±15.53*	102.77±24.1*	113.76±20.69*	102.26±23.87*
Admission glucose	160.48±78.8	135.93±54.86*	169.09±84.08*	138.59±68.41*	173.72±82.87*	148.65±79.31*	174.45±76.22*	163.21±71.81	160.09±79.91	179.79±72.21*	155.42±79.85*
Onset-needle time	169.55±54.79	158.85±65.29*	174.01±50.06*	160.36±64.48*	175.11±47.39*	166.12±58.97	173.60±49.38	171.79±48.46	169.23±55.74	167.04±56.85	170.21±54.38

(*P<.05, SD, standart deviation; NIHSS, National Institute of Healt Stroke Scale; MAP, Mean Arterial Pressure)

Table 2: The initial NIHSS scores and changes during follow-up in different ischemic stroke subtypes. There was no significant difference between groups (P>.05)

	Number (%)	Admission NIHSS (Mean±SD)	Day 1 NIHSS change (Mean±SD)	Day 7 NIHSS change (Mean±SD)	Day 90 NIHSS change (Mean±SD)
All patients	231 (100%)	13.48±5.96	2.91±5.51	2.6±9.78	1.27±14.5
LAA	80 (34.63%)	11.97±4.8	3.5±4.08	3.5±8.69	1.91±13.54
CE	120 (51.95%)	15.2±6.29	2.36±6.43	1.54±10.97	0.33±15.74
Lac	8 (3.46%)	7.62±3.25	2.38±3.42	3.25±3.62	5.37±3.58
Others	23 (9.96%)	11.83±5.55	3.91±5.21	4.73±7.85	5.22±12.54

(LAA, Large artery atherosclerosis; CE, Cardioembolism; Lac, Lacunar infarct; SD, Standart deviation; NIHSS, National Institute of Health Stroke Scale Score)

Table 3: The impact of search parameters on recovery, mortality and complication rates after IV-tPA infusion in acute ischemic stroke (ORs are given from the multivariate analysis)

Variable (n)	Day 1 Good responder n (%)	OR (95%CI)	Day 7 Good responder n (%)	OR (95%CI)	Day 90 Good responder n (%)	OR (95%CI)	Intracranial hemorrhage n (%)	OR (95%CI)	Mortality n (%)	OR (95%CI)
Total	60 (25.97%)		87 (37.66%)		125 (54.11%)		29 (12.55%)		48 (20.78%)	
Age>70 (88)	18 (20.45%)	0.341 (0.147-0.792)	26 (29.54)	0.439 (0.211-0.914)	34 (38.64%)**	0.386 (0.192-0.775)	12 (13.64%)	0.661 (0.245-1.784)	26 (29.54%)	1.572 (0.695-3.552)
Age≤70 (143)	42 (29.37%)		61 (42.66%)		91 (63.19%)		17 (11.89%)		22(15.38)	
Male (136)	40 (29.41%)	1.818 (0.832-3.974)	58 (42.65%)	1.553 (0.786-3.068)	85 (62.50%) *	1.962 (1.023-3.765)	17 (12.50%)	0.892 (0.338-2.352)	23 (16.91%)	0.621 (0.276-1.397)
Female (95)	20 (21.05%)		29 (30.53%)		40 (42.51%)		12 (12.63%)		25 (26.32%)	
MAP>105 mmHg(107)	21 (25.30%)	0.852 (0.392-1.850)	29 (34.94%)	0.782 (0.387-1.579)	39(46.99)	0.628 (0.323-1.222)	18(21.68%)*	4.398 (1.586-12.193)	23 (27.71%)	1.795 (0.808-3.990)
MAP≤105 (83)	26 (24.29%)		40 (37.38%)		61 (57.01)		7 (6.54%)		17(15.89%)	
Subtype		0.784 (0.509-1.208)		0.946 (0.647-1.384)	41 (51.25%)	1.219 (0.832-1.784)		0.710 (0.304-1.662)	1	0.850 (0.474-1.524)
LAA (80)	23 (28.75%)		31 (38.75%)		61 (50.83%)		7 (8.75%)		4 (17.50%)	
CE (120)	30 (25%)		43 (35.83%)		6 (75%)		22 (18.33%)*		32 (26.67%)	
Lac (8)	1 (12.50%)		2 (25.00%)		17 (73.91%)		0 (0%)		0 (0%)	
Others (23)	6 (26.09%)		11 (47.83%)				0 (0%)		0 (0%)	
Onset-to-needle		0.436 (0.251-0.756)		0.492 (0.299-0.810)		0.641 (0.396-1.037)		1.274 (0.817-2.633)		1.079 (0.612-1.901)
0-89 minutes (24)	11 (45.83%)*		16 (66.67%)**		17 (70.83%)		1 (4.17%)		5 (20.83%)	
90-179 minutes(120)	32 (26.67%)		42 (35%)		63 (52.50%)		18 (15.00%)		26 (21.67%)	
180-270 minutes(85)	16 (18.82%)		27 (31.76%)		43 (50.59)		10 (11.76%)		17 (20.00%)	
>270 minutes(2)	1 (50%)		2 (100%)		2 (100%)		0 (0%)		0 (0%)	

(*:P<.05, **:P<.01, MAP, Mean arterial pressure; Glu, glucose; LAA, Large artery atherosclerosis; CE, Cardioembolism; Lac, Lacunar infarct, OR, Odds Ration; CI, Confidence Interval)

At the end of 90 days, patients with decrease in NIHSS scores more than 7 or reaching a final NIHSS score below 3 were significantly younger (good responders 62±12 versus poor responders 70±11 at day 90) and had significantly lower admission blood glucose levels (good responders 149±79 versus poor responders 174±76, P<.05, Table 1). The novel significant parameters were age and gender after adjustment, the rate of good response at 3 months was significantly higher in male patients and in patient younger than 70 [P<.01, OR;95% CI:0.386 (0.192-0.775) for being younger than 70, P<.05, OR;95% CI:0.492 (0.257-0.941) for female gender, Table 3]. There was no significant difference among remaining research parameters including ischemic stroke subtype (P>.05, Table 3).

The average length of hospital stay was 17±25 (r:1-307) days. Length of stay was significantly lower in small vessel disease group (19 days for LAA, 17 days for CE, 7 days for SVD, 13 days for others group). The rate of patients with mRS 0-1 at the discharge was significantly higher in SVD group (50% in the SVD and 43% in the others groups versus 8% in the LAA and 21% in the CE groups, P<.05). In the aspects of secondary end points; 48 patients (20.8%) died at the end of 90 days. Systemic infusion of tissue type plasminogen activator resulted 29 intracranial haemorrhages (12.6%), 3 extracranial haemorrhages (1.3%) and 2 mild allergic reactions (0.9%). Only 7 intracranial haemorrhages were symptomatic (3%) and 4 were fatal (1.7%). None of the patients with lacunar infarcts died at the end of 3 months. 32 of 120 cardioembolic patients (26.7%) and 14 of the 80 stroke patients with large vessel disease (17.5%) were lost within 3 months, however the difference did not reach significance (Table 3). Similarly mRS at discharge and 90th day was not significantly different among different stroke subtypes, the rate of patients with mRS 0-1 was similar between groups (P>.05). None of the patients with SVD and infarcts due to other causes had experienced an intracranial haemorrhage after systemic tPA administration. The rate of intracranial haemorrhage due to IV-tPA was significantly more common in cardio embolic strokes (18.3%) (P<.05, Table 3).

High admittance mean arterial pressure and NIHSS scores were other significant predictors of intracranial bleeding (P<.05, Table 1). Also cerebral bleeding as a complication of thrombolytic treatment was significantly more common in patients with atrial fibrillation (P<.05, Table 3). Multivariate analysis revealed significant risk of high emergency room blood pressure and atrial fibrillation for intracranial haemorrhage [P<.01, OR;95% CI:5.085 (1.734-14.906) for atrial fibrillation, P<.01, OR;95% CI:4.398 (1.586-12.193) for mean arterial pressure>105mmHg]. Other complications (extracranial haemorrhage and allergic reactions) occurred very rarely, not allowing a statistical evaluation.

Mortality rate at the end of 3 months was significantly higher in elderly patients. Admission blood glucose levels, mean arterial blood pressure values and NIHSS scores were significantly higher in patients who died within 3 months (P<.05, Table 1). Ischemic stroke subtype was not correlated with mortality rates (P>.05, Table 3). Mortality rate was also higher in patients with coronary artery disease and atrial fibrillation (P<.05, Table 3). However, these significances were lost in multivariate analysis, only accompanying coronary heart disease increased the cumulative risk of mortality in 90 days after adjustment [P<.01, OR;95% CI:0.244 (0.089-0.670)]. Other parameters are not correlated with mortality rates.

DISCUSSION

The main target of thrombolytic treatment for acute ischemic stroke is to break up the clot and re-construct blood flow at the site of penumbra. The benefit of this treatment on clinical outcomes has been proven in large prospective clinical trials with a mild tendency to intracranial bleeding. Beyond, 26-36% of the patients who receive standard of care in a stroke unit without fibrinolysis reach to favourable outcome (mRS 0-1) after 3 months.[1,9] Thirty three percent of patients treated with alteplase in the first 3 hours and 35.3% of patients treated between 3-4.5 hours reach to an excellent mRS (mRS:0-1) after 3 months.[10] In our study, one fourth of the patients reached an excellent recovery within the first 24 hours, and one third of our patients gained good recovery with in the first one week. In daily practice at the emergency room, the first goal of the neurologist is to find the patient who will benefit the most and the fast, with minimal risk of harm and to determine the patient whose symptoms will resolve spontaneously. A couple of factors which facilitate the impact of IV-tPA and reduce the risk of haemorrhage were described. The best defined parameters which increase the effectiveness of systemic thrombolysis are short onset-to-needle duration and well preserved collateral flow, besides, high admission blood sugar and blood pressure are known to increase risk of intracranial bleeding.[3,5,6]

Beyond these, the origin of the clot may be important for recanalization and good outcome. Several endovascular clot retrieval trials supported rapid recanalization rates in the presence of erythrocyte rich fresh clots compared to fibrin rich old clots.[11,12] Clots derived from large arteries are shown to be larger and more resistant to retrieval due to their cellular components.[13] Dense MCA sign, if present in the early phase, may disappear after thrombolytic treatment if the clots origin is the heart.[14,15] Platelet rich old clots are more resistant to thrombolysis compared to fibrin and blood cell rich clots. Fresh clots formed during stasis are more degradable than chronic clots circulating through the bloodstream.[7,12,16] Erythrocyte–fibrin-rich thrombi are the targets of thrombolytic agents.[17] On the other side, the underlying pathophysiological mechanism may not be thrombogenic in lacunar strokes, so a good response to tPA may not be expected in small vessel disease. The occlusion of small perforating arterioles leading to lacunar infarcts are the result of lipohyalinosis and microatheromas.[18] Lipohyalinosis is caused by widespread deposition of fibrous connective tissue destroying the integrity of intima and media, and leading occlusion of small vessel lumen, so it may not be expected to be recanalised by enzyme activated fibrinolysis.[19,20] So, the etiologic origin of cerebral vessel occlusion may be a predictor of good or bad response to systemic thrombolysis.

In the current study, we tried to determine the efficacy of IV-tPA in different ischemic stroke etiologic subtypes together with risk of complications in the early and late phases. Though lesion characteristics on diffusion-weighted imaging (DWI), rapid computed tomography angiography (CTA) and electrocardiography (ECG) may give clues about stroke etiology, the thrombolyzed patients in our hospital are not routinely separated according to etiology before the thrombolysis decision, and etiologic evaluation is done later on. The first randomised controlled trial of alteplase, the NINDS trial, revealed no difference in the rates of patients reaching to favourable outcome at the end of 3 months among different ischemic stroke subtypes.[21] The impact of stroke subtype on outcomes is not clearly evaluated in ECASS.[2,9] The results of our study demonstrated that the proportion of patients achieving a dramatic good response after systemic fibrinolytic treatment at the 1st, 7th and 90th days was quite similar between large arterial atherosclerosis and cardioembolic groups. The small group of patients with SVD showed a lower rate of serious improvement in the early phase (one week), but 75% of SVD patients reach perfect recovery at the end of 3 months. Strokes due to other rare causes improve even in the early and late stages quite similar to other groups even after adjustment.

The present literature on this argument is conflicting. This may be due to the variability of definition of favourable response and follow-up period. In concordance with our results, the largest data coming from Madrid Stroke Network also conclude that the stroke subtype has no influence on outcome at the end of 3 months after systemic tPA administration.[22] Rocha et al found no difference in outcomes of cardioembolic and non cardioembolic strokes at the first day and discharge in a 177 patient cohort from Portugal.[7] Similarly, the analysis of Austrian Stroke Unit Registry revealed no difference between different stroke subtypes.[23]

Besides, the retrospective analysis of 572 Danish patients revealed a higher incidence of reaching NIHSS score of 0 or reduction over 3 at the 24th hour in cardioembolic strokes compared to stroke due to large vessel disease.[24] Another retrospective evaluation of 827 Chinese patients showed a better outcome in cardioembolic stroke at the end of three months compared to large vessel strokes.[25] A previous study including 303 patients revealed a better but non-significant response in cardioembolic patients against non-cardioembolic group. The same study demonstrated a better improvement with IV-tPA in younger patients with milder stroke severity.[26] Similar improvement was detected in the cardioembolic group at the 24th and 72nd hours in another small study.[15] An analysis of 256 patients with dense MCA sign receiving IV-tPA demonstrated a better early improvement in cardioembolic patients against LAA patients at the end of one week.[14] Cardioembolic infarctions may benefit more from IV tPA than other aetiologies, even in young patients.[27] In another trial, quite oppositely, cardio embolism is found to be the predictor of disability and death at the end of 3 months, even in the mild stroke patients receiving IV-tPA.[28]

There are also evidence of good response to IV-tPA for the small vessel disease strokes in the present literature. Analysis of the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis (SITS-IST) registry revealed higher incidence of excellent outcome in the lacunar infarctions compared to non-lacunar strokes at the end of 3 months. Intracranial haemorrhage rate is found to be lower in SVD.[29,30] Excellent outcome defined as mRS 0-1 or Barthel Index 95-100 at the end of 3 months was found to be more common in small vessel disease against cardioembolic and large arterial atherosclerotic stroke, together with null intracranial haemorrhages and mortality in several other studies.[31] Larger studies showed also better beneficial effects and lower haemorrhagic complications in small vessel disease patients compared to cardioembolic and large arterial atherosclerosis patients.[32] Mustanoja et al.[33] demonstrated that the best outcome is present in patients with small vessel disease after thrombolytic treatment, in their retrospective analysis of 957 patients from Helsinki Stroke Thrombolysis Registry. Just similar with our results, they found no death and intracranial bleeding in lacunar infarct group.[33] Besides, some trials demonstrate greater benefit in non-lacunar strokes[34] and in some no difference.[23]

Patients with strokes due to large arterial atherosclerosis benefit more from systemic thrombolysis if they have NIHSS scores below 5. IV-tPA may be beneficial in patients with large vessel atherosclerosis because of the prevention thrombus propagation and early worsening.[35]

Aside from the subtype, the basic determinants of excellent improvement in the first 24 hours and the first week were admission blood glucose level and onset-to-needle time according to our results. Patients with blood glucose level lower than 180 mg/dl on the emergency court, and patients who receive alteplase intravenously within the first 90 minutes have 2-3 fold chance of dramatic early good response. Good response rate was more common in men and younger patients at the end of 3 months.

Large systematic reviews report the mortality rate to be 22.2% if IV-tPA is given within first 3 hours and, 16.9% if given between 3-4.5 hours in large reviews. Intracranial haemorrhage is seen in 3.7% of patients.[10] These rates are in concordance with our data. Mortality and intracranial haemorrhage rates were reported to be higher in cardioembolic strokes.[25,32,36] Our data also demonstrated high early intracranial haemorrhage rate in patients whose blood pressure is high at admittance. Strokes due to cardioembolism or atrial fibrillation have higher risk of intracranial bleeding after systemic fibrinolytic treatment. Presence of cerebral micro bleeds is known to cause intracerebral bleeding after administration of IV-tPA.[37,38] High infarct volume and weak collateral flow may be a reason of high rate of hemorrhagic transformation in cardioembolic strokes.[25] Also, hyperglycaemia is a predictor of worse outcome after thrombolytic treatment. This effect is more prevalent in non-lacunar strokes.[15]

The major limitation of our study was the retrospective design and low number of patients, especially in specific subtypes. The reason of this is probably the status of our institution as a tertiary care stroke centre, so that mild stroke cases may not be referred to our hospital even in the acute phase. Especially the rate of patients with SVD was too low for secure statistical results. Also, the results of the current study should be evaluated cautiously because the data covers only the experience of a single centre.

CONCLUSION

We found that there is no difference in the proportion of patients who gain a dramatic reduction of NIHSS score more than 7 after systemic IV-tPA infusion for acute ischemic stroke management on day 1, 7 and 90 between different etiologic stroke subtypes. The major determinants of early excellent recovery seem to be admission blood sugar and onset-to-needle time. Withholding thrombolysis in patients with definite subtypes has not been recommended in acute ischemic stroke setup.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Ondokuz Mayıs University (Date: November 11, 2019; Decision No: OMU KAEK 2019/758). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: In this retrospective study, the requirement for informed consent was waived by the ethics committee due to the use of anonymized pre-existing data.

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