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Comparative Analysis of Tertiary Stroke Center: Factors Affecting the 3rd Month Clinical Outcome of Patients Treated with Thrombolytic Treatment

Üçüncü Basamak İnme Merkezinin Iv-tPA Deneyimi: Trombolitik Tedavi Uygulanan Hastalarda 3. Ay Klinik Sonlanıma Etki Eden Faktörler

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ABSTRACT

Objective: In this study, we aimed to document the data of intravenous thrombolytic therapy [intra venous tissue plasminogen activator (iv-tPA)] that we applied to patients admitted to our stroke unit with acute ischemic stroke, and to verify the correlation of these data with the 3rd month modified Rankin Scale (mRS) score.

Methods: We enrolled 235 patients in the study who were admitted to İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital with acute ischemic stroke and received iv-tPA. Demographic data of the patients and stroke risk factors were recorded. Trial of Org 10172 in acute stroke (TOAST) classification for stroke etiology, Bamford stroke classification to define stroke clinic, "National Institute of Health Stroke Scale" score to evaluate stroke severity, and "the Alberta stroke program early CT" (ASPECT) score to evaluate the brain tomography of patients before iv-tPA were used. The 3rd month functional outcomes were evaluated with the mRS score. The correlation between all data obtained from the patients and mRS score was examined.

Results: Two hundred thirty five patients who received iv-tPA (128 females, 107 males, mean age 72.23±13.88) were included in the study. It was observed that patients with atrial fibrillation rhythm and patients who developed complications during hospitalization had significantly higher mRS scores. When the relationship between TOAST classification subgroups and mRS score was examined, it

ÖZ

Amaç: Bu çalışmada inme ünitemize akut iskemik inmeyle başvuran hastalara uyguladığımız intravenöz trombolitik tedavi [intravenous tissue plasminogen activator, (iv-tPA)] verilerini dokümante etmeyi ve bu verilerin 3. ay modifiye Rankin Skalası (mRS) skoru ile korelasyonunu incelemeyi amaçladık.

Yöntemler: İstanbul Medeniyet Üniversitesi Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi İnme Ünitesi'ne akut iskemik inme ile başvuran ve iv-tPA uygulanan 235 hasta çalışmaya alındı. Hastaların demografik verileri ve inme risk faktörleri kaydedilmiştir. İnme etiyolojisi için Trial of Org 10172 in acute stroke (TOAST) sınıflaması, inme kliniğini tanımlamak için Bamford inme sınıflaması, inme şiddetini değerlendirmek amacıyla "National Institute of Health Stroke Scale", iv-tPA öncesi hastaların beyin tomografisini değerlendirmek için "The Alberta stroke programme early CT score" (ASPECT) skoru kullanılmıştır. Hastaların 3. ay sonundaki fonksiyonel sonlanımları mRS skoru ile değerlendirilmiştir. Hastaların elde edilen tüm verileri ile mRS skoru arasındaki korelasyon bakılmıştır.

Bulgular: Çalışmaya iv-tPA tedavisi alan 235 hasta (128 kadın, 107 erkek, yaş ortalaması 72,23±13,88) dahil edilmiştir. Yatış komplikasyonu gelişen ve atrial fibrilasyon ritmi olan hastaların mRS skorlarının anlamlı şekilde daha yüksek olduğu görüldü. TOAST sınıflaması alt gruplarıyla mRS arasındaki ilişkiye bakıldığında,

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was found that the large artery atherosclerosis and cardioembolism groups had higher mRS score than the small vessel disease and undetermined etiology groups. According to the Bamford classification, the total anterior circulation syndrome group had a higher mRS score than all other groups. A negative correlation was detected between ASPECT score and mRS score.

Conclusion: As a result of this study, Bamford and TOAST classifications, ASPECT score, the presence of atrial fibrillation rhythm, and the development of complications during hospitalization were important factors in predicting 3rd month disability of the patients who were treated with iv-tPA.

Keywords: Thrombolytic therapy, modified rankin scale, disability, stroke

büyük arter aterosklerozu ve kardiyoembolizm gruplarının, küçük damar hastalığı ve etiyolojisi belirlenemeyen gruplara göre daha yüksek mRS 3 değerlerine sahip olduğu bulundu. Bamford sınıflamasına göre Tacs grubu diğer tüm gruplardan daha yüksek mRS skoruna sahipti. ASPECT skoru ve mRS skoru arasında negatif korelasyon tespit edildi.

Sonuç: Bu çalışmada elde edilen verilere göre trombolitik tedavi verilen hastaların Bamford ve TOAST sınıflamalarının, ASPECT skorunun, atrial fibrilasyon ritminin varlığının ve yatış komplikasyonunun gelişmesinin hastaların 3. aydaki engelliliğini tahmin etmede önemli faktörler olduğu sonucuna varılmıştır.

Anahtar Sözcükler: Trombolitik tedavi, modifiye rankin skalası, engellilik, inme

Introduction

Ischemic stroke, known as incurable for a long time, has reached an exciting point thanks to proven treatments that have taken their place in neurology practice in the last decades (1). Intravenous tissue plasminogen activator (iv-tPA) and mechanical thrombectomy have taken their place in clinical practice as treatment options that have proven to have a great effect on mortality and morbidity of stroke. With these treatment methods, it is aimed to provide recanalization and reperfusion in brain tissue with impaired oxygenation and protect the penumbra. Thus, it is aimed to restore the brain functions lost due to stroke and to prevent additional neural damage that may occur in the following hours. Recently, the prevalences of the main risk factors for ischemic stroke such as sedentary lifestyle habits, obesity which was becoming a global public health problem, and drug and tobacco use have increased. Thus, the importance of acute stroke management and treatment practices is increasing (2). Despite the increase in the prevalence of stroke, ischemic stroke has regressed from the 3rd most common cause of death worldwide to the 5th place in recent years, thanks to the acute interventions that have been developed (3). The biggest obstacle to treatments is the inability of patients to reach stroke centers where they can receive appropriate treatment during the acute intervention period. Today, the majority of stroke patients cannot receive acute treatment because they are not admitted to the hospital in the appropriate time (4). The time window of treatment, which was determined as the first three hours for intravenous thrombolytic therapy, was extended to the first 4.5 hours with the stroke guideline updated in 2013, and the number of studies supporting that this treatment can be given up to 9 hours in selected patients are increasing (5-7). In the stroke guidelines, the importance of pre-hospital organization, establishing in-hospital stroke teams, and evaluation of patients with tele-medicine before they come to the hospital are emphasized in order to give appropriate treatment to the patients during these periods (6).

In this study, we documented the data of iv-tPA treatment that we gave to patients who were admitted with acute ischemic stroke since the stroke unit was established in our hospital (2018-2021) and the correlation of these data with the 3rd month modified Rankin Scale (mRS) score, by categorizing the patients according to the time intervals of treatment (0-3 hours, 3-4.5 hours and >4.5 hours).

Methods

For this study, the Ethics Committee approval was obtained from İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision number 2021/0187 and date 10.03.2021. We enrolled 235 patients in the study who were admitted to İstanbul Medeniyet University Göztepe Training and Research Hospital Stroke Unit with acute ischemic stroke and received iv-tPA between January 2018 and May 2021. The medical records of the patients were reviewed retrospectively, and demographic (age, gender) and clinical data (vascular risk factors, symptom-door, door-needle times, undergoing thrombectomy after iv-tPA, complications due to iv-tPA, complications during hospitalization) were obtained. Cranial tomography and craniocervical CT angiography were performed in all patients as the protocol of the stroke center before iv-tPA. At the 24th hour after iv-tPA, control imaging was obtained with tomography or cranial magnetic resonance imaging with gradient echo sequence. Patients were categorized into three groups according to treatment time intervals (0-3 hours, 3-4.5 hours and >4.5 hours). Iv-tPA was given after 4.5 hours only to the patients in the wake-up stroke category in which the onset of symptoms was unclear, and when diffusion FLAIR mismatch was detected.

The TOAST (Trial of Org 10172 in acute stroke) classification for stroke etiology, Bamford stroke classification to define stroke clinic, "National Institute of Health Stroke Scale" (NIHSS) score (acute period - discharge - 1st month) to evaluate stroke severity, "the Alberta stroke program early CT" (ASPECT) score to evaluate the brain tomography of patients before iv-tPA were used. The functional outcomes of the patients at the end of the 3rd month were evaluated with the mRS score. Patients with mRS 0-2 were determined as having good outcome, and patients with mRS 3-6 were determined as having poor outcome. All the data obtained were subjected to comparative analysis with the mRS score.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used. The distribution of the data were evaluated with the Shapiro-Wilk Test. Kruskall-Wallis test was used for comparison of quantitative data of three or more groups; Mann-Whitney U Test was used for comparison of two groups. Linear regression analysis was used to determine the factors affecting the dependent variable. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

Results

Two hundred thirty five patients who received iv-tPA (128 females, 107 males, mean age 72.23±13.88) were included in the study. The stroke risk factors and etiological classification data of the patients are given in Table 1. Admission NIHSS scores did not show statistically significant difference according to iv-tPA delivery time ($p>0.05$). It was found statistically significant that the admission NIHSS score of the thrombectomy group was higher than the group that did not undergo thrombectomy ($p=0.001$ and $p<0.01$) (Table 2).

Table 3 contains data on the relationship between stroke risk factors and mRS score. It was found statistically significant that the 3rd month mRS score of the patients who developed complication during hospitalization was higher than the group without complication ($p=0.001$ and $p<0.01$). The 3rd month mRS score of the group with AF was found to be statistically significantly higher than the group without AF ($p=0.001$ and $p<0.01$) (Table 3). The mRS scoreat the 3rd month showed a statistically significant difference between iv-tPA application times ($p=0.044$ and $p<0.05$). The 3rd month mRS score of the group that received iv-tPA within 0-3 hours was statistically significantly higher than that of the group that received iv-tPA within 3-4.5 hours ($p=0.001$ and $p<0.05$). Considering the relationship between TOAST classification subgroups and mRS score, large artery atherosclerosis (LAA) group and cardioembolism group were found to have higher mRS score than small vessel disease and undetermined etiology groups ($p=0.001$ and $p<0.05$). In the Bamford classification, TACS group had a higher mRS score than all other groups ($p=0.001$ and $p<0.05$). It was observed that the 3rd month mRS scores of the thrombectomy group were significantly higher than the group that did not undergo thrombectomy ($p=0.001$ and $p<0.01$) (Table 4).

In Table 5, the multiple linear regression analysis was performed to determine the effect of independent variables on the 3rd month mRS score ($F=18.628$, $p<0.001$). There was a positive and highly significant relationship between independent variables and 3rd month mRS score ($R=0.725$, $p<0.01$). The independent

Table 1. The stroke risk factors and etiological classification data of the patients

		n	%
Sex	Female	128	54.5
	Male	107	45.5
Hypertension	No	55	23.4
	Yes	180	76.6
Hyperlipidemia	No	131	55.7
	Yes	104	44.3
Diabetes mellitus	No	151	64.3
	Yes	84	35.7
Atrial fibrillation	No	142	69.8
	Yes	93	30.2
Smoking	No	164	69.8
	Yes	71	30.2
iv-tPA	0-3 hours	159	67.7
	3-4.5 hours	65	27.7
	>4.5 hours	11	4.7
TOAST classification	Large artery atherosclerosis	34	14.9
	Small vessel oclusion	39	17.1
	Cardioembolism	118	51.8
	Undetermined etiology	37	16.2
Bamford classification	Tacs	9	3.9
	Pacs	154	67.2
	Pocs	41	17.9
	Lacs	23	10.0
	Mixed	2	0.9

iv-tPA: Intravenous tissue plasminogen activator, TOAST: Trial of Org 10172 in acute stroke

variable in the model explains 52.5% of the total variance of the 3rd month mRS score (p<0.01). When the regression coefficients were examined, the ASPECT score (β=-0.122, p<0.01) had a negative effect on the 3rd month mRS score; age (β=0.18, p<0.01), complications during hospitalization (β=0.49, p<0.01) and thrombectomy (β=0.153, p<0.01) had a positive and significant effect on the 3rd month mRS score (Table 5).

Discussion

In this study, we aimed to analyze the data of patients who received iv-tPA treatment within 3 years in our stroke center and to observe the effect of these data on the 3rd month disability score. The presence of AF and complications due to hospitalization had a negative effect on the 3rd month mRS score. It was observed that the 3rd month mRS scores of the small vessel disease group in the TOAST classification and the lacunar syndrome (Lacs) group in the Bamford classification were significantly lower than the other groups. The 3rd month mRS score was found to be significantly higher in the patients who underwent thrombectomy. This was attributed to the significantly higher NIHSS scores at admission in this patient group due to LAA.

Patients who received iv-tPA between 3-4.5 hours had lower mRS scores at 3 months compared to the group that received iv-tPA in the first three hours. Although this result contradicts the knowledge that the sooner patients receive iv-tPA treatment, fewer neurons will die and the pneumbra will be more protected, we see that patients who receive treatment within the first 3 hours have higher admission NIHSS scores.

In the lineer regression analysis data, a significant direct correlation was found between age and 3rd month mRS score. As the age progresses, the effectiveness of treatment is lower and the disability in the 3rd month is higher. As expected, the ASPECT score was inversely correlated, and patients with higher ASPECT scores had lower mRS 3 scores because they started treatment with more preserved brain tissue. Complications due to

Table 2. Patients' admission NIHSS scores

		NHISS scores		
		Mean ± SD+	Min-max (median)	P
iv-tPA time	0-3 hours	9.62±5.66	2-24 (8)	0.191[a]
	3-4.5 hours	8.58±5.74	2-22 (6)	
	>4.5 hours	7.27±3.35	3-15 (7)	
Thrombectomy	No	8.05±5.01	2-24 (7)	0.001**[b]
	Yes	13.87±5.5	4-23 (15)	

[a]Kruskall-Wallis Test, [b]Mann-Whitney U Test, NIHSS: National Institute of Health Stroke Scale, iv-tPA: Intra venous tissue plasminogen activator, *p<0.05, **p<0.01, Mean ± SD+: Mean ± standard deviation

Table 3. Relationship of stroke risk factors with 3rd month mRS score

		3rd Month mRS score		
		Mean ± SD+	Min-max (median)	P
Sex	Female	1.94±2.22	0-6 (1)	0.926
	Male	1.89±2.09	0-6 (1)	
Complication during hospitalization	No	1.11±1.56	0-6 (0)	0.001**
	Yes	4.13±2	0-6 (5)	
Hypertension	No	1.58±2.04	0-6 (0)	0.144
	Yes	2.02±2.19	0-6 (1)	
Hyperlipidemia	No	2.07±2.29	0-6 (1)	0.453
	Yes	1.72±1.96	0-6 (1)	
Diabetes mellitus	No	1.98±2.18	0-6 (1)	0.618
	Yes	1.8±2.12	0-6 (1)	
Atrial fibrillation	No	1.45±1.83	0-6 (1)	0.001**
	Yes	2.61±2.43	0-6 (2)	
Coronary artery disease	No	1.71±2.03	0-6 (1)	0.084
	Yes	2.32±2.36	0-6 (2)	
Smoking	No	2.05±2.2	0-6 (1)	0.070
	Yes	1.59±2.02	0-6 (0)	
Drug addiction	No	1.92±2.16	0-6 (1)	0.290
	Yes	0±0	0-0 (0)	

Mann-Whitney U *p<0.05, **p<0.01, Mean ± SD+: Mean ± standard deviation

Table 4. Relationship of stroke data with 3rd month mRS score

		3rd Month mRS score		
		Mean ± SD+	Min-max (median)	P
t-PA administration	0-3 hours	2.07±2.21	0-6 (1)	0.044**a
	3-4.5 hours	1.39±1.87	0-6 (0)	
	>4.5 hours	2.73±2.53	0-6 (2)	
TOAST classification	Large artery atherosclerosis	2.39±2	0-6 (3)	0.001**a
	Small vessel oclusion	0.64±1.06	0-4 (0)	
	Cardioembolism	2.48±2.34	0-6 (2)	
	Undetermined etiology	1.11±1.76	0-6 (0)	
Bamford classification	Tacs*	5.11±1.17	3-6 (6)	0.001**a
	Pacs*	2.27±2.22	0-6 (2)	
	Pocs*	0.78±1.24	0-6 (0)	
	Lacs*	0.74±1.21	0-4 (0)	
	Miks	0±0	0-0 (0)	
Use of antiplatelet/ anticoagulant	No	1.82±2.22	0-6 (1)	0.741a
	Antiplatalet	2.02±2.05	0-6 (1.5)	
	Anticoagulant	2±2.27	0-6 (1)	
	Both	2.5±3.54	0-5 (2.5)	
Complication due to iv-tPA	No	1.86±2.14	0-6 (1)	0.136b
	Yes	2.59±2.29	0-6 (2)	
Thrombectomy	No	1.57±1.93	0-6 (1)	0.001**b
	Yes	3.33±2.47	0-6 (3.5)	

aKruskall-Wallis Test, bMann-Whitney U Test, *p<0.05 **p<0.01, +Tacs: Total anterior circulation syndrome, Pacs: Partial anterior circulation syndrome, Pocs: Posterior circulation syndrome, Lacs: Lacunar syndrome. Mean ± SD+: Mean ± standard deviation

Table 5. Linear regression analysis findings for the relationship between independent variables and 3rd month mRS score

		Univariable					Multivariable				
Model	Variables	B	SD+	Standard (B)	t	p	B	SD	Standard (B)	t	p
1	Age	0.052	0.010	0.335	5.411	0.001**	0.028	0.008	0.18	3.4	0.001**
	ASPECT score	-0.655	0.154	-0.269	-4.262	0.001**	-0.296	0.12	-0.122	-2.466	0.001**
	Hospitalization Complication-Yes	3.021	0.25	0.623	12.108	0.001**	2.375	0.25	0.49	9.491	0.001**
	AF-Yes	1.159	0.279	0.263	4.160	0.001**					
	Thrombectomy	1.757	0.336	0.324	5.223	0.001**	0.833	0.282	0.153	2.95	0.001**
	iv-tPA-3-4.5 hours	-0.721	0.313	-0.149	-2.300	0.001**					
	Toast-small vessel occlusion	-1.528	0.366	-0.265	-4.179	0.001**					
	Toast-cardioembolism	1.147	0.272	0.266	4.209	0.001**					
	Toast-Undetermined	-0.958	0.382	-0.162	-2.506	0.001**					
	Bamford-TACS	-0.802	0.162	-0.310	-4.966	0.001**					
	Bamford-PACS	1.021	0.289	0.226	3.528	0.001**					
	Bamford-POCS	-1.375	0.361	-0.243	-3.813	0.001**					
	Bamford-LACS	-1.304	0.467	-0.180	-2.792	0.001**					

*p<0.05, **p<0.01, +SD: Standard deviation

hospitalization in stroke patients are a major factor on mortality and morbidity. As a result of this study, it was concluded that the 3rd month disability of the patients with complications due to hospitalization was higher.

The mRS constitutes one of the most reliable scales used globally to score the third month endpoint outcome in stroke patients (8). It also shows the success of acute stroke treatments by showing the disability and dependence of the patients in the third month after the stroke (9). In a meta-analysis by Li et al., (10) the effect of early mobilization on acute stroke patients was examined with mRS score, and it was shown that the shorter hospital stay was associated with better outcomes. Similarly, in this study, complication due to hospitalization was shown to be associated with worse mRS scores.

The most avoided complication of acute thrombolytic therapy is bleeding. Intracerebral hemorrhage, which develops as a treatment complication, is associated with high mortality (10). Complications of symptomatic intracranial hemorrhage were reported at a rate of 2.4% in the European Cooperative Acute Stroke Study 3 (ECASS 3) and 7% in the "Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Study" (11,12). Similar to the literature, bleeding complications were observed after iv-tPA in 7.23% of the patients. As a result of this study, no significant difference was observed between the patient groups who developed and did not develop iv-tPA bleeding complications in terms of 3rd month mRS scores.

As a result of the stroke project conducted by Antonio Di Carlo et al. (13), it was observed that the risk of death at the 3rd month significantly increased in total anterior circulation infarctions (TACI) group patients compared to lacunar infarctions group patients. In the same study, it was shown that atrial fibrillation was predictive for TACI (13). In this study, it was observed that the mRS score of the patients in the LAA and TACS (total anterior circulation syndrome) groups were significantly lower. The presence of atrial fibrillation also had a significant negative effect on mRS score.

In the ECASS-4 study, iv-tPA treatment was given to acute stroke patients between 4.5 and 9 hours who met the criteria of infarct core volume <100 mL, perfusion lesion: infarct core mismatch ratio >1.2 and perfusion lesion minimum volume of 20 mL. As a result of the study, it was reported that the time of administration of thrombolytic therapy could be extended in selected patients (7). No treatment complications were observed in 11 patients included in this study who were given iv-tPA >4.5 hours and they benefited from the treatment. There was no significant difference between the 3rd month mRS scores of the three groups. This result led us to the conclusion that thrombolytic therapy should be given to selected patients in support of ECASS-4 (7).

Study Limitations

For more efficient statistical analysis, the number of patients given iv-tPA >4.5 hours should be higher. Likewise, the retrospective design of the study creates a limitation in terms of accessing patient data.

Conclusion

Iv-tPA is a safe and effective treatment for acute stroke. Clinical stroke classifications and defining stroke risk factors during acute stroke are useful in estimating the 3rd month mRS score.

Ethics

Ethics Committee Approval: For this study, the Ethics Committee approval was obtained from İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision number 2021/0187 and date 10.03.2021.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.K., R.Ş., D.Ç., S.Ö., Z.T.Y., O.İ., K.A., Concept: H.H.K., R.Ş., O.İ., K.A., Design: R.Ş., D.Ç., Data Collection or Processing: R.Ş., D.Ç., S.Ö., Analysis or Interpretation: H.H.K., O.İ., K.A., Literature Search: R.Ş., Writing: R.Ş.

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