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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

INTRAVENOUS THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE:

A SINGLE CENTER EXPERIENCE

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ABSTRACT

INTRODUCTION: Intravenous (iv) thrombolytic therapy is used in the acute phase of stroke to recanalize the occluded vessel and provide reperfusion.The aim of this study is to determine the frequency of side effects and prognosis and the affecting factors in the patients who received iv thrombolytic therapy with the diagnosis of acute ischemic stroke in the neurology clinic of a state hospital between December 2016 and December 2019.
METHODS: After obtaining the necessary ethical and institutional permissions, 181 patients who were diagnosed with acute ischemic stroke and received iv thrombolytic therapy in the Neurology Clinic of Denizli State Hospital between December 2016 and December 2019 were analyzed. In this retrospective cohort type study, data were collected with a standart form. Intracranial hemorrhages occurring within the first 36 hours after the treatment were considered as complications of the treatment. The 6th month modified Rankin Stroke Scale (mRS) data of the patients were calculated.
RESULTS: The mean age of the patient was 67.8 (±12.7) years and 72 (39.8%) were female. Over the years, the number of treatments increased from 29 to 71. There was a history of recurrent CVO in 39 (21.0%) patients. Mean symptom/door time 86±50 min, door/needle time 93±47 min, and symptom/needle time 179±56 min. Only 34 (18.8%) patients were given normal dose of r-tPA. Intracranial hemorrhage was observed in 24 (13.3%) of the patients after treatment. Factors affecting intracranial hemorrhage after treatment were ASPECT score (26.9% in patients with ≤7, 7.8% in patients with ≥8, $p<0.001$), infarct type (35.3% in TACI+PACI, 0% in LACI patients), $p=0.002$) and NIHSS 24-hour value (0% in mild cases, 32.3% in severe cases, $p<0.001$). Factors that affecting the prognosis at the 6th month after treatment were ASPECT score, type of infarct, NIHSS level at admission, 24-hour NIHSS level, mRS at discharge level and mRS level at 1 month.
DISCUSSION AND CONCLUSION: Our results were generally found to be compatible with similar studies published in Turkey and the number of patients receiving iv thrombolytics has been increasing over the years. However, it is noteworthy that iv thrombolytics were used at low doses in this study. This suggests that there may be a need for in-service training on iv thrombolytics.
Keywords: Stroke, thrombolytic therapy, prognosis, bleeding, death.

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AKUT İSKEMİK İNMEDE İNTRAVENÖZ TROMBOLİTİK TEDAVİ: TEK MERKEZ DENEYİMİ

ÖZ

GİRİŞ ve AMAÇ: İntravenöz (iv) trombolitik tedavi inmenin akut döneminde tıkalı damarı rekanalize etmek ve reperfüzyonu sağlamak için uzun bir süredir kullanılmaktadır. Bu araştırmanın amacı Aralık 2016 ve Aralık 2019 yılları arasında bir devlet hastanesi Nöroloji kliniğinde akut iskemik inme tanısı ile iv trombolitik tedavi almış hastaların tedaviye bağlı yan etki sıklığını ve prognozlarını ve etkileyen faktörleri belirlemektir.

YÖNTEM ve GEREÇLER: Gerekli etik ve kurum izinleri alındıktan sonra Aralık 2016 ve Aralık 2019 yılları arasında Denizli Devlet Hastanesi Nöroloji kliniğinde akut iskemik inme tanısı konulan ve iv trombolitik tedavi uygulanan 181 hasta incelendi. Retrospektif kohort epidemiyolojik düzenindeki araştırmamızda veriler standart bir form ile toplandı. Tedavi sonrası ilk 36 saat içerisinde meydana gelen intrakraniyal kanamalar tedaviye bağlı komplikasyon olarak değerlendirildi. Hastaların 6. ay modifiye Rankin Stroke Skalası (mRS) verileri hesaplandı.

BULGULAR: Çalışmaya alınan 181 hastanın yaş ortalaması 67,8 (±12,7) yıl ve 72'i (%39.8) kadındı. Yıllar içinde tedavi sayıları 29'dan 71'e çıktı. Semptom-kapı zamanı ortalaması (SD) 86±50 dk, kapı-iğne zamanı 93±47 dakika ve semptom-iğne zamanı 179±56 dk idi. Sadece 34 (%18,8) hastaya iv trombolitik normal dozda verildi. Tedavi sonrası hastaların 24'ünde (%13,3) intrakraniyal kanama gözlendi. Tedavi sonrası intrakraniyal kanamayı etkileyen faktörler olarak ASPECT skoru (≤7 olanlarda %26,9 iken, ≥8 olanlarda %7,8, p<0,001), infarkt tipi (TACI+PACI olanlar %35,3 iken, LACI olanlar %0, p=0,002) ve NIHSS 24 saat değeri (hafif olanlarda %0 iken, ağır olanlarda %32,3, p<0,001) olarak saptandı. Tedavi sonrası 6. ay prognozu olumlu olarak etkileyen faktörler; ASPECT skoru, infakt tipi, başvurudaki NIHSS seviyesi, 24. saat NIHSS seviyesi, taburculuktaki mRS seviyesi ve 1. aydaki mRS seviyesi idi.

TARTIŞMA ve SONUÇ: Sonuçlarımız genel olarak Türkiye'den yayınlanan benzer çalışmalar ile uyumlu bulunmuştur ve yıllar içinde iv trombolitik alan akut inmeli hasta sayıları artmaktadır. Fakat bu çalışmada iv trombolitiğin çoğunlukla düşük dozlarda kullanıldığı dikkat çekmektedir. Bunun sebeplerinin araştırılması ve gerekirse hizmet içi eğitim planlanmalıdır.

Anahtar Sözcükler: İnme, trombolitik tedavi, prognoz, kanama, ölüm.

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability-adjusted life-year losses globally (1). In the last four decades, the incidence of stroke has doubled in low- and middle-income countries (2). Intravenous (iv) thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA) has long been used in the acute phase of stroke to re-channel the occluded vessel and provide timely reperfusion (3). Evidence on this treatment began in 1995, with the study of "The National Institute of Neurological Disorders and Stroke (NINDS)" demonstrating the efficacy of IV thrombolytic therapy in patients with acute ischemic stroke within the first 3 hours (4). Studies following this NINDS study also confirmed this treatment to be effective and safe (5). Today, its use is recommended in acute ischemic stroke within 4 to 5 hours of symptom onset (6). Although the drug was licensed for use in acute ischemic stroke in Turkey in 2006, the use of this treatment is still not at the desired level (7).

With this study, it was aimed to present the epidemiological data of acute ischemic stroke patients who received iv thrombolytic therapy in Denizli province, the second largest city in the Aegean region, and to contribute to our country's data on acute stroke treatment with clinical practice. Denizli State Hospital was defined as a Stroke Center within the scope of a project carried out by the Denizli Provincial Health Directorate during its working years, and all patients with a preliminary diagnosis of stroke were referred 24/7 by 112 Emergency Service. This practice was initiated in 2016, and in the same year, iv thrombolytic therapy was also adopted as a routine procedure in our Pamukkale University Faculty of Medicine, Department of Neurology under the coordination of the provincial health directorate. This study aimed to determine the incidence of treatment-related short and long-term side effects and affecting factors in patients who received iv thrombolytic therapy (Recombinant tissue plasminogen activator (r-tPA)) with the diagnosis of acute ischemic stroke in the Denizli State Hospital Neurology Clinic between December 2016 and December 2019.

METHODS

After obtaining the necessary permissions, demographic and clinical data of 181 patients who

were diagnosed with acute ischemic stroke in the Denizli State Hospital, Neurology Clinic between December 2016 and December 2019 and were treated with iv thrombolytic therapy within the first 4 to 5 hours of symptom onset and wake-up stroke (WUS), that is stroke with unknown onset time, were analyzed retrospectively. Ethics committee approval numbered 01.10.2020-E.59519 was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee (No: 60116787-020/59519, Date: 01.10.2020), and institutional permissions were obtained from Denizli Health Directorate and Denizli State Hospital Hospital. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

In this retrospective cohort epidemiological study, data were collected with a form prepared based on the existing literature and the American Heart Association/American Stroke Association 2019 guideline published by the Turkish Neurological Society Cerebrovascular Diseases study group. In this treatment routine, patients who did not have absolute contraindications or their relatives were informed about the benefits and possible complications of the treatment, and their consent was obtained. Sociodemographic data such as age, gender, height, weight, smoking and alcohol habits, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, coronary artery disease and previous ischemic stroke history, symptoms at admission, time between the onset of stroke symptoms and admission to hospital (onset-to-door time (ODT), time between admission to hospital and initiation of treatment (door-to-needle time (DNT)), time between stroke symptom onset and treatment initiation (onset-needle time (ONT)), presence of antiaggregant or anticoagulant use during stroke, neurological examination findings and laboratory findings were recorded. Neurological examination and computed tomography (CT) findings and, if necessary, CT angiography or magnetic resonance (MR) angiography tests were determined before and 24 hours after treatment initiation in all patients. In patients with deterioration in neurological examinations, CCT was repeated without waiting 24 hours to determine whether hemorrhagic transformation developed.

The “National Institutes of Health Stroke Scale” (NIHSS) averages of all patients were calculated before and 24 hours after the treatment (8). The NIHSS is an eleven-item scale that examines neurological functions in patients with acute stroke and provides insight into long-term prognosis. A total of 0-42 points are obtained by evaluating five main parameters. These 5 parameters are level of consciousness, visual evaluation, language-motor functions, sensory-neglect and cerebellar functions (9). In the NIHSS, normal/near-normal examination was classified as 0 points, mild stroke 1-4 points, moderate stroke 5-14 points, moderate/severe stroke 15-20 points, and severe stroke 21 and above (10). In this study, patients with a mean NIHSS score of 0-4 before starting thrombolytic therapy and 24 hours after treatment were classified as mild, 5-20 as moderate, and 21 or more as severe stroke.

In addition, Alberta Stroke Program Early CT Scores (ASPECTS) (11) of each patient were recorded. ASPECTS is a 10-point quantitative scoring system used to rapidly assess early ischemic changes in the middle cerebral artery (MCA) irrigation area on non-contrast CT. The ASPECTS score of the affected hemisphere is calculated by subtracting a total of 1 point for each ischemia-affected area in the MCA irrigation area. Lower ASPECTS values indicate a larger infarct area. Similarly, the PC-ASPECTS scoring system was established to predict the clinical response of posterior circulation acute ischemic strokes (12).

Strokes were classified as TACI (total anterior circulation infarction), PACI (partial anterior circulation infarction), LACI (lacunar infarction), and POCI (posterior circulation infarction) according to the Oxfordshire Community Stroke Project (OCSP) (13). OCSP aims to facilitate a definitive prognosis prediction at an early stage. In addition, the patients' modified Rankin Stroke Scale (mRS) data at the 1st and 6th months were calculated. mRS allows the assessment of the patient's dependence on others and functional recovery. Out of a total of six points, a score of three or more indicates poor prognosis and the patient's dependence on others in daily activities (14). In the present study, mRS classifications were as follows; 0-2 mild, 3-4 moderate, and 5 and death severe.

In the present study, “symptomatic” intracranial hemorrhage was detected on CT after r-tPA treatment, and an increase of 4 points or more in NIHSS according to ECASS criteria, and “asymptomatic” intracranial hemorrhage was defined as incidentally detected bleeding in

control imaging without clinical and NIHSS worsening (15). Intracranial hemorrhage occurring within the first 36 hours after treatment were considered complications of IV r-tPA.

Before treatment, two intravenous vascular accesses were opened for each patient, and nasogastric and bladder catheters were placed. Arterial interventions with antiaggregant and anticoagulant treatment were not applied in the first 24 hours. In patients who received 0.9 mg/kg (maximum 90 mg) iv r-tPA, 10% of the total calculated dose was given as an iv bolus and the remainder as an infusion in 1 hour (16), and although there is no predetermined protocol in the literature, 147 patients (81.2%) received low dose (0.6 mg/kg) IV r-tPA at the initiative of the neurologist. Echocardiography (Echo), electrocardiogram (ECG) and carotid/vertebral artery Doppler ultrasonography (USG) were performed on hospitalized patients.

Statistical analysis: Categorized data were presented as numbers and percentages, and continuous data as mean and standard deviation or median and min-max. Factors affecting intracranial hemorrhage and 6th month prognosis were tested with nonparametric tests (Mann-Whitney U and Kruskal Wallis). $p<0.05$ was considered significant.

RESULTS

The mean age of the 181 patients included in the study was 67.8 (±12.7) (min-max, 19-88) years, and 72 (39.8%) were women. A history of recurrent cerebrovascular event (CVE) was present in 39 (21.5%) patients. Fifty-two (28.7%) patients had ASPECTS scores of 7 and below. Patients were classified according to infarct type as follows: 87 (48.1%) were PACI, 26 (14.4%) were TACI, 42 (23.2%) were POCI, 17 (9.4%) were POCI+TACI, and 9 (5.0%) were LACI. In 132 (72.9%) patients, the NIHSS value decreased in 24 hours compared to admission. There was a 51% or more decrease in NIHSS values in the first 24 hours in 74 (40.9%) patients. The mean symptom/door (S/D) time was 86±50 min, the door/needle (D/N) time was 93±47 min, and the symptom/needle (S/N) time was 179±56 min. (Table 1).

Only 34 (18.8%) patients were given a normal dose of r-tPA, and 24 (13.3%) had post-treatment intracranial hemorrhage. Of the patients with intracranial hemorrhage, 10 (5.5%) had symptomatic hemorrhage, while 11 (6.0%) had Stage 1, 3 (1.6%) had Stage 2, 2 (1.1%) had Stage 3, and 8 (4.4%) had Stage 4 hemorrhage. Forty-four (24.3%) of the patients died during the 6-month follow-up. After treatment, 4 (2.2%) patients died within the first 24 hours, 3 (1.7%) at second day, and 2 (1.1%) patients at third day. The mRS outcomes were severe and death was seen in

Table 1. The sociodemographic and clinical characteristics of the patients, and timing of treatment.

	Mean	SD
Age, year	67,8	±12,7
	n	%
Gender, Female	72	39,8
CVE history, Yes	39	21,5
ASPECT, mean±SD	8,1	±2
ASPECT group		
7 and below	52	28,7
8 and above	129	71,3
Years		
2016	29	16,0
2017	44	24,3
2018	37	20,4
2019	71	39,2
Enfarct type		
LACI	9	5,0
PACI	87	48,1
POCI	42	23,2
TACI	26	14,4
TACI/POCI	17	9,4
NIHSS admission, mean ±SD	11,9	±6,1
NIHSS admission		
Mild (0-4)	6	3,3
Moderate (5-20)	152	84,0
Severe (21 and above)	23	12,7
NIHSS 24 hour, mean ±SD	9	±8,9
NIHSS 24 hour		
Mild (0-4)	73	40,3
Moderate (5-20)	77	42,5
Severe (21 and above)	31	17,1
NIHSS change		
Increase	37	20,4
No increase or decrease	12	6,6
Decrease	132	72,9
NIHSS change percentage		
Decrease of 51% or more	74	40,9
Decrease of 25-50%	40	22,1
Decrease of 1-24%	18	9,9
No change	12	6,6
Increase of 1-24%	19	10,5
Increase of 25-50%	9	5,0
Increase of 51% or more	9	5,0
Symptom/Door (S/D) time (min)	86	50
Door/Needle (D/N) time (min)	93	47
Symptom/Needle (S/N) time (min)	179	56

ASPECTS: Alberta Stroke Program Early CT Score; TACI: Total anterior circulation infarction; PACI: Partial anterior circulation infarction; LACI: Lacunar infarction; POCI: Posterior circulation infarction; NIHSS: The National Institutes of Health Stroke Scale.

41 (22.6%) patients in the 1st month and in 45 (24.6%) patients in the 6th month (Table 2).

Table 2. Distribution of patients' drug doses and prognoses (death, hemorrhage, NIHSS and mRS over time).

	n	%
Drug doses		
Lower (0,6 mg/kg)	147	81,2
Normal (0,9 mg/kg)	34	18,8
Intracranial hemorrhage, Yes	24	13,3
Intracranial hemorrhage		
Asymptomatic	14	7,7
Symptomatic	10	5,5
Intracranial hemorrhage stage		
1	11	6,0
2	3	1,6
3	2	1,1
4	8	4,4
Mortality, death	44	24,3
Death time		
1st day	4	2,2
2nd day	3	1,7
3rd day	2	1,1
4-30. gün	24	13,3
31-180 gün	11	6,1
mRS 1st month		
0-2 mild	115	63,5
3-4 moderate	25	13,8
5 severe or death	41	22,6
mRS 6th month		
0-2 mild	115	63,5
3-4 moderate	21	11,6
5 severe or death	45	24,8

mRS: Modified Rankin Stroke Scale; NIHSS: The National Institutes of Health Stroke Scale.

Factors affecting the presence of intracranial hemorrhage after treatment statistically significantly were identified as the ASPECT score [hemorrhage in 14 (26.9%) patients with ASPECT≤7, in 10 (7.8%) patients with ASPECT ≥8, (p<0.001)], the infarct type [(hemorrhage in 6 (35.3%) patients with TACI+POCI, 0 (0%) patients with LACI, (p=0.002)], and the NIHSS 24-hour values [(hemorrhage in 4 (5,5%) patients with mild, and 10 (32.3%) patients with severe score (p<0.001)] (Table 3).

Factors positively affecting the prognosis (mRS) at 6 months after treatment were as follows; mean age [mean (±SD) age 66.5 (12.5) years in mRS=0-2 mild patients, 72.4 (12.8) years in mRS=5 severe and death patients, p=0.02)], ASPECT score [mRS=0-2 mild in 18 (34.6%) with ASPECT ≤7 and 96 (74.4%) with ASPECT ≥8, p<0.001)], type of infarct [mRS=0-2 mild in 7 (77.8%) with LACI and in 2 (11.8%) with TACI+POCI 2, p<0.001)], admission NIHSS

Table 3. Factors affecting intracranial hemorrhage.

	Hemorrhage Yes N=24, n(%)	Hemorrhage No N=157, n(%)	P
Age, years, Mean (SD)	67,2 (11,6)	67,9 (12,8)	0,7
Gender			
Male	16 (14,7)	93 (85,3)	0,639
Female	8 (11,1)	64 (88,9)	
CVE history			
Yes	6 (15,4)	33 (84,6)	0,861
No	18 (12,7)	124 (87,3)	
ASPECT group			
7 and below	14 (26,9)	38 (73,1)	0,001
8 and above	10 (7,8)	119 (92,2)	
Drug dose			
Low (0,6 mg/kg)	19 (12,9)	128 (87,1)	0,7
Normal (0,9 mg/kg)	5 (14,7)	29 (85,3)	
Infarct typr			
LACI	0 (0)	9 (100)	
PACI	7 (8,0)	80 (92,0)	
POCI	3 (7,1)	39 (92,9)	
TACI	8 (30,8)	18 (69,2)	0,002
TACI/POCI	6 (35,3)	11 (64,7)	
Arrival NIHSS			
Mild (0-4)	0 (0)	6 (100)	
Moderate (5-20)	19 (12,5)	133 (87,5)	0,297
Severe (21 and above)	5 (21,7)	18 (78,3)	
NIHSS 24 hour			
Mild (0-4)	4 (5,5)	69 (94,5)	
Moderate (5-20)	10 (13,0)	67 (87,0)	0,001
Severe (21 and above)	10 (32,3)	21 (67,7)	
Symptom/Needle (S/N) time (min)	179±55	179±60	0,9

NIHSS: The National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; mRS: modified Rankin Stroke Scale.

[mRS=0-2 in 6 (100%) with mild NIHSS, mRS=0-2 in 4 (17.4%) with severe NIHSS, p<0.001)], 24th hour NIHSS [mRS=0-2 in 71 (97.3%) with mild NIHSS, mRS=0-2 in 2 (6.5%) with severe NIHSS, p<0.001], and 1st month mRS [6th month mRS=0-2 in 111 (96.6%) with mild 1st month mRS, 6th month mRS=0-2 in 0 (0%) with severe 1st month mRS, p<0.001] (Table 4).

DISCUSSION AND CONCLUSION

This study presented the results of patients who received iv thrombolytics for acute ischemic stroke from a state hospital designated as a regional stroke center. Over the years covered by the study, there was a notable increase in the number of patients receiving iv thrombolytic therapy due to ischemic stroke at Denizli State Hospital. In recent years, iv r-tPA application in acute ischemic stroke has become increasingly common in Turkey, as in all over the world (7). Yet, even studies conducted in developed countries have reported that this treatment is not

Tablo 4. Factors affecting the prognosis at 6 months after treatment.

	mRS 6th month			P
	0-2 mild n (%)	3-4 moderate n (%)	5 severe or death n (%)	
Age, years, Mean (SD)	66,5 (12,5)	65,7 (11,7)	72,4 (12,8)	0,02
Gender				
Male	71 (65,1)	11 (10,1)	27 (24,8)	0,6
Female	43 (59,7)	10 (15,9)	19 (26,4)	
CVE history				0,09
Yes	21 (53,8)	3 (7,7)	15 (38,5)	
No	93 (65,5)	18 (12,7)	31 (21,8)	
ASPECT				<0,001
7 and below	18 (34,6)	9 (17.3)	25 (48,1)	
8 and above	96 (74,4)	12 (9,3)	21 (16,3)	
Drug dose				
Low (0,6 mg/kg)	92 (62,6)	18 (12,2)	37 (25,2)	0,8
Normal (0,9 mg/kg)	22 (64,7)	3 (8,8)	9 (26,5)	
Infarct type				<0,001
LACI	7 (77,8)	1 (11,1)	1 (11,1)	
PACI	65 (74,7)	11 (12,6)	11 (12,6)	
POCI	30 (71,4)	3 (7,1)	9 (21,4)	
TACI	10 (38,5)	4 (15,4)	12 (46,2)	
TACI/POCI	2 (11,8)	2 (11,8)	13 (76,5)	
Arrival NIHSS				<0,001
Mild (0-4)	6 (100)	0 (0)	0 (0)	
Moderate (5-20)	104 (68,4)	20 (13,2)	28 (18,4)	
Severe (21 or above)	4 (17,4)	1 (4,3)	18 (78,3)	
NIHSS 24 hour				<0,001
Mild (0-4)	71 (97,3)	0 (0)	2 (2,7)	
Moderate (5-20)	41 (53,2)	21 (27,3)	15 (19,5)	
Severe (21 and above)	2 (6,5)	0 (0)	29 (93,5)	
mRS 1th month				<0,001
0-2 mild	111 (96,5)	2 (1,7)	2 (1,7)	
3-4 moderate	3 (12)	19 (76)	3 (12)	
5 severe or death	0 (0)	0 (0)	41 (100)	
Symptom/Needle (S/N) time (min)	179±54	175±60	182±60	0,8

TACI: Total anterior circulation infarction; PACI: Partial anterior circulation infarction; LACI: Lacunar infarction; POCI: Posterior circulation infarction; ASPECTS: Alberta Stroke Program Early CT Score; mRS: modified Rankin Stroke Scale; NIHSS: The National Institutes of Health Stroke Scale.

sufficiently available to patients (17,18). The patient's lack of information about stroke symptoms, lack of health infrastructure to provide thrombolytic treatment to stroke patient, the emergency department physician's lack of knowledge on stroke symptoms, invalid contraindications and difficulties in accessing the drug have been frequently mentioned in the medical literature as obstacles to the patient's timely access to appropriate treatment (19-21). Further work is needed to ensure that all eligible patients have access to this vital treatment in the future.

The present study found that the vast majority of patients received low-dose IV thrombolytics. Although the existing medical literature indicates that high doses of iv r-tPA increase the risk of intracranial bleeding, how the use of the drug at less than the licensed doses affects the effectiveness of the drug is still unknown (22). Likewise, low-dose administration is not included in the diagnosis and treatment guidelines of the Ministry of Health in acute ischemic stroke in Turkey (16). Therefore, the drug is expected to be used in full dose. Although this issue has not been addressed in other studies conducted in Turkey, we believe that a few of our hypotheses on why neurologists in the field are not using the full dose of thrombolytic therapy can guide future research. Our experience is that the main reason for this approach may be the neurologists' fear that any bleeding complication may cause problems such as the patient not being able to find a place in the intensive care unit, losing the patient, being sued for malpractice, and perhaps being exposed to the violence of the patient's relatives. Another possible reason may be the problems with accessing the drug from time to time in hospitals in Turkey, and finally, an effort to avoid opening the second vial required to give the full dose, i.e., using 5cc and throwing away the remaining 45cc. Future research on this subject should determine the obstacles in reaching the appropriate dose of the drug for all patients suitable for iv r-tPA and propose necessary interventions to eliminate these obstacles.

In this study, treated patients' mean S/N time and D/N time was 179 minutes and 93 minutes, respectively, which are longer those reported by similar studies in Turkey. A study from Kutahya found the mean S/N time as 149 minutes and the mean D/N time as 72 minutes aproximately (23). In another study conducted in Istanbul, the mean S/N time was 169 minutes and the D/N time was 81 minutes (24). According to the data of the Turkish Thrombolytic Treatment Study Group, these times were 150 and 69 minutes, respectively (7). In this regard, we think that it would be appropriate to raise the patients' knowledge and awareness about stroke through public education in our region, as well as the physicians' awareness and skills with in-service training programs.

In our study, all intracranial hemorrhages constituted 13.3% of the treatments, while

symptomatic ones comprised only 5.5%. Internationally, symptomatic intracranial hemorrhages have been reported with a rate of 6.4% in NINDS, 2.4% in ECASS 3, and 7% in ATLANTIS-B (25-27). A multicenter study by Yaghi et al. reported symptomatic intracranial hemorrhage development in 128 (3.3%) of 3,894 patients who received iv thrombolytics (28). Studies conducted in Turkey reported rates of 3.8%, 15.6% and 16% (23,29,30). Our patients' post-treatment intracranial hemorrhage rates are similar to some of these published results. The differences between the results may be attributed to the mentioned studies being international intervention studies testing the efficacy and side effects of the drug under "ideal conditions", while our research reveals the "real life" use of the drug. In addition, in our study, drug dose was not included among the factors affecting intracranial hemorrhage after treatment. We think that this data can also help convince neurologists working in the field, who are hypersensitive to early intracranial hemorrhage, to administer the medication in full dose.

In our study, approximately one-fourth of the cases were lost during the 6-month follow-up. Mortality rates were higher in international studies; 17% in the 3-month follow-up in the NINDS study, 7.7% in ECASS 3, and 11% in ATLANTISB (22-24). On the other hand, a study conducted in Kutahya, Turkey, reported a mortality rate of 25%, similar to our findings (23). This rate was reported as 14.7% by the Turkish Thrombolytic Treatment Study Group (7). A few possible reasons for the difference in mortality rate between our study and the mentioned studies may be the nature of the studies, i.e., international studies are intervention studies, so that the efficacy and side effects of the drug are revealed in "ideal conditions" and ours in "real life", as well as differences in the follow-up period, time, sample group, and location.

Our study revealed an improvement in NIHSS scores after iv r-tPA treatment, indicating the effectiveness of the treatment in the acute period in stroke patients. Similarly, the above mentioned study conducted in Kütahya, which compared the NIHSS scores of all patients in the acute period before and at the 24th hour after treatment, reported a statistical decrease in NIHSS scores after treatment (p=0.001) (23). In our study, good long-term prognosis after treatment was 63.5%. In the NINDS and ECASS 3 study, good long-term prognosis rates were 39% and 52%, respectively (25,26). However, in another study from Turkey, the rate of patients with mRS in the 0-1 range 3 months after treatment was reprted to be only 30.8% (23).

The biggest limitation of our study is the retrospective data collection process. As in all retrospective studies based on records, there may be an incorrect grouping of participants due to inaccurate and incomplete records. However, this possibility is quite low since ischemic stroke and its protocols are a well-known and standardized concept among neurologists. Nevertheless, moderate-to-large sample size is one of the strengths of this study. Another strength of our research is that it reports a longer prognosis (6 months). Finally, although low-dose therapy is not included in the guidelines, as our literature research has revealed, a randomized controlled intervention study with mostly Asian participants found no difference in prognosis between the standard and low-dose groups, and even noted significantly lower intracranial hemorrhages in those receiving low-dose drugs (31). Along with this evidence, the lack of difference in intracranial hemorrhages and 6-month prognosis in the low-dose group compared to the standard dose in our study may serve as a warning for further research on this subject. Scientifically determining the low dose as effective and safe will reduce the cost of drugs and enable access to medicine in developing countries like ours.

In conclusion, our findings are consistent with similar studies published in Turkey and are noteworthy because the number of stroke patients receiving IV thrombolytics has increased over the years. In particular, this study also drew attention to the use of low doses of iv thrombolytics in clinical practice. The reasons for this preference should be investigated and, if necessary, in-service training should be planned.

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Ethics

Ethics Committee Approval: The study was approved by Pamukkale University Non-Interventional Ethical Committee (No: 60116787-020/59519, Date: 01.10.2020).

Informed Consent: The author declared that informed consent was not obtained from the patients because of the retrospective study design.

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