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Experience of Intravenous Thrombolytic Treatment in Sanliurfa: A Prospective Study

Şanlıurfa'da İntravenöz Trombolitik Tedavi Deneyimi: Prospektif Bir Çalışma

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Abstract

Objective: Stroke ranks second among the diseases that cause death and third among the causes of disability in Turkey. An average of 1.9 million neurons die every minute due to acute ischemic stroke and therefore 'time is brain'. Intravenous thrombolytic treatment (ITT) and, if possible, endovascular treatment should be initiated quickly. We aimed to share our ITT experience in Sanliurfa with this study.

Materials and Methods: We recorded the clinical and demographic characteristics, risk factors, and three-month follow-up of 21 patients with acute ischemic stroke who were given ITT between June 2015 and July 2017.

Results: Of the 21 patients, nine were male and 12 were female, and the mean age was 72.1±11.8 (range, 48-87) years. Large vessel occlusion was found in five (23.8%) patients, cardioembolism in 9 (42.9%), and small vessel occlusion in 2 (9.5%) patients; etiology was not determined in five (23.8%) patients. Atrial fibrillation was found in 38.1%, hypertension in 57.1%, diabetes mellitus in 23.8%, coronary artery disease in 33.3%, hyperlipidemia in 19%, and smoking in 33.3% of the patients.The NIHSS score was 11.7±6.7 (range, 2-24) prior to treatment. The symptom-onset to needle time was 185±55.8 minutes when 19 patients were evaluated. Intracerebral hemorrhage was observed in two (9.5%) patients after treatment. One patient was asymptomatic and the symptomatic patient (4.75%) died despite decompression surgery. Ten patients died and the mortality rate was 47.6% at the end of the three-month follow-up period. The modified Rankin scale score was 0-2 in eight patients (38.1%) and was 0-1 in seven patients (33.3%). ITT was given to seven patients aged ≥80 years, five patients with NIHSS <5, and two patients in whom the treatment window was exceeded, which was non-adherent to the label.

Conclusion: ITT is effective and safe. It increases the number of independent living patients. We must strive to perform this treatment all over Turkey and encourage our colleagues.

Keywords: Acute ischemic stroke, intravenous thrombolytic treatment, outcome

Öz

Amaç: İnme, Türkiye'de ölüme neden olan hastalıklar içerisinde ikinci sırada ve özürlülüğe yol açan nedenler içerisinde üçüncü sıradadır. Akut iskemik inmeye (Aİİ) bağlı her geçen dakikada ortalama 1,9 milyon nöron ölmektedir ve bu nedenle "zaman beyindir". Hızlı bir şekilde intravenöz trombolitik tedaviye (İTT) ve mümkünse endovasküler tedaviye başlanmalıdır. Biz bu çalışma ile Şanlıurfa'daki İTT deneyimimizi paylaşmayı amaçladık.

Gereç ve Yöntem: Haziran 2015 ve Temmuz 2017 arasında başvuran, Aİİ tanısı konarak İTT verilen 21 hastanın klinik ve demografik özelliklerini, risk faktörlerini ve 3 aylık izlemlerini kaydettik.

Bulgular: Çalışmaya dahil edilen 21 hastanın 12'si kadın, 9'u erkekti ve yaş ortalamaları 72,1±11,8 (48-87) idi. Etiyolojik incelemede hastaların beşinde (%23,8) büyük damar hastalığı, dokuzunda (%42,9) kardiyoembolizm, ikisinde (%9,5) küçük damar hastalığı saptanırken, beşinde (23,8%) neden bulunamadı. Hastaların %38,1'inde atrial fibrilasyon, %57,1'inde hipertansiyon, %23,8'inde diabetes mellitus, %33,3'ünde koroner arter hastalığı, %19'unda hiperlipidemi ve %33,3'ünde sigara kullanımı mevcuttu. Hastaların tedavi öncesi National Institutes of Health Stroke Scale (NIHSS) skoru 11,7±6,7 (2-24) idi. Semptom başlangıcından tedaviye başlanana kadar geçen süre 19 hasta değerlendirildiğinde 185±55,8 dakika idi. İki hastada (%9,5) tedavi sonrası intraserebral kanama gözlendi. Birisi asemptomatikti, semptomatik (%4,75) olan bir hasta ise dekompresif cerrahi uygulanmasına rağmen kaybedildi. Üç aylık takipte on hasta kaybedildi ve mortalite oranı (%47,6) olarak hesaplandı. Üçüncü ay modifiye Rankin skalası skoru, sekiz hastada (%38,1) 0-2, yedi hastada (%33,3) 0-1 idi. Yedi hastada ≥80 yaş, beş hastada NIHSS <5 ve iki hastada 4,5 saatlik tedavi penceresi aşılmış olmasına rağmen, ruhsatlandırma dışı olarak İTT uygulanmıştır.

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Öz

Sonuç: İTT etkili ve güvenlidir. Bağımsız yaşayan hasta sayısını anlamlı olarak arttırır. Bu tedavinin Türkiye'nin her yerinde uygulanmasına gayret göstermeli ve meslektaşlarımızı cesaretlendirmeliyiz.

Anahtar Kelimeler: Akut iskemik inme, intravenöz trombolitik tedavi, sonlanım

Introduction

For every second that a large vessel occlusion is not treated, 32,000 neurons die and this number corresponds to the amount of neurons that the brain loses in 8.7 hours with normal aging. When the occlusion ends with an infarction, an average of 1.2 billion neurons die and this number corresponds to the amount of neurons that the brain loses in 36 years with normal aging (1). For this reason, 'time is brain' and intravenous (IV) thrombolytic therapy (ITT) and if possible, endovascular treatment should be started quickly.

Acute ischemic stroke (AIS) caused approximately 2.8 million deaths and 39.4 million disability-adjusted life years (DALYs) in 2010 (2,3). AIS is responsible for 15% of all deaths in Turkey and is the second most frequent cause of death. In addition, it is the third most frequent cause of disability in Turkey, with a rate of 5.9% DALYs (4). ITT with alteplase was approved by the United States Food and Drug Administration (FDA) in 1996 and has since been used in the treatment of AIS in the first step all over the world. In Turkey, alteplase was approved in 2006 and the first national study was published in 2016 (5).

In this study, we aimed to share our experience of ITT in Sanliurfa with the literature.

Materials and Methods

In this study, 21 of 23 adult patients with AIS who were treated with ITT only and were admitted to Mehmet Akif Inan Training and Research Hospital between June 2015 and July 2017 were included. Two patients were excluded because they received mechanical thrombectomy following ITT. Demographic characteristics, risk factors, duration between onset of symptoms until ITT was given, etiologies of patients, National Institutes of Health Stroke Scale (NIHSS) scores at 0 and 24 hours, modified Rankin scale (mRS) scores pre-stroke, at discharge/ one week after discharge and at three months after discharge, and complications were recorded. Informed consent was obtained from the patients or their relatives before ITT was given. This study was approved by the local ethics committee of Local Ethics Committee of Mehmet Akif Inan Training and Research Hospital.

In order to classify the stroke etiologies of the patients, the classification defined in the Trial of Org 10172 in Acute Stroke Treatment was used (6). In patients who developed cerebral hemorrhage after ITT, the classification described in European Cooperative acute stroke Study 2 (ECASS 2) was used to classify the bleeding (7).

The accordance of the patients for ITT was determined according to the current stroke guidelines. ITT was given to the patients who were admitted within 4.5 hours after the onset of symptoms, and the patients were evaluated by taking into consideration the inclusion and exclusion criteria after the exclusion of bleeding in cranial computed tomography (CT). In addition to cranial CT, diffusion magnetic resonance imaging (MRI) was also performed in approximately half of the patients in the emergency room. Due to a lack of technical equipment, only one patient was able to receive cranial CT angiography in the acute period. Patients with an NIHSS score higher than six and without bleeding in cranial CT and acute infarction in diffusion-weighted MRI suggesting large vessel occlusion were referred to the Department of Neurology at Harran University Training and Research Hospital for endovascular treatment, if possible. The patients in whom ITT was contraindicated and who were referred for endovascular treatment, and patients who were referred for endovascular treatment after ITT were excluded.

ITT was performed in all patients in the neurology or anesthesia intensive care unit (ICU). Twenty four hours after ITT was given, control cranial CT was performed in all patients. Cranial and cervical MRI angiography or carotid-vertebral artery doppler ultrasonography were performed in all patients. In adddition, each patient underwent a cardiac examination [electrocardiogram, transthoracic echocardiogram (ECHO), 24-hour rhythm Holter and transesophageal ECHO, if necessary], and lipid profile and routine blood examinations were performed. Stable patients were followed up in the neurology ward and physical therapy and rehabilitation were provided in cases where necessary.

The mRS scores at three months were calculated by examining the patients or through phone interviews. Patients with mRS scores of 0-2 were accepted as having good outcomes, and patients with mRS scores 3-6 were accepted as having poor outcomes.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 statistics package. The relationship between age, sex, time between the onset of symptoms and the onset of ITT, NIHSS scores, risk factors, etiology and outcomes were investigated using the chi-square test. A p value of <0.05 was considered statistically significant.

Results

Of the 21 patients included in the study, 12 were female and 9 were male. The mean age was 72.1±11.8 (range, 48-87) years. Five (23.8%) of the patients had large vessel disease, nine (42.9%) had cardioembolism, two (9.5%) had small vessel disease, and no etiology was found in five (23.8%) patients. Atrial fibrillation was detected in 38.1% of patients with stroke as a risk factor. Data of other risk factors were obtained in about 70% of the patients due to a lack of records. According to the data, hypertension was recorded in 57.1% of patients, diabetes mellitus in 23.8%, coronary artery disease in 33.3%, hyperlipidemia in 19%, and smoking in 33.3%. The mean pre-treatment NIHSS score of the patients was 11.7±6.7 (range, 2-24). Excluding the two patients who were treated with ITT beyond the treatment window, the mean time between the

onset of symptoms and the onset of ITT was 185±55.8 minutes in 19 patients. The clinical and demographic features and risk factors of the patients are summarized in Table 1. In addition, the characteristics of each patient are shown in the Table 2.

Table 1. Demographic and clinical features and risk factors

Age, mean ± SD (min-max)	72.1±11.8 (range, 48-87) years
Sex, n (%)	
Male	9 (42.9%)
Female	12 (57.1%)
Stroke type, n (%)	
Large vessel disease	5 (23.8%)
Cardioembolic	9 (42.9%)
Small vessel disease	2 (9.5%)
Unknown	5 (23.8%)
Symptom-needle time*, mean ± SD	185±55.8 minutes
NIHSS at admission, mean ± SD (min-max)	11.7±1.5 (range, 2-24)
NIHSS at 24 hours, mean ± SD (min-max)	10.1±1.8 (range, 0-25)
mRS-pre-stroke, mean ± SD (min-max)	0.43±1 (range, 0-3)
mRS-at discharge/at 1 week, mean ± SD (min-max)	3.5±2 (range, 0-6)
mRS-at 3 months, mean ± SD (min-max)	3±2.6 (range, 0-6)
Complication, n (%)	
Yes	2 (9.5%)
No	19 (90.5%)
Risk factors, n (%)**	
Atrial fibrillation	
Yes	8 (38.1%)
No	13 (61.9%)
Hypertension	
Yes	12 (57.1%)
No	3 (14.3%)
Diabetes mellitus	
Yes	5 (23.8%)
No	10 (47.6%)
Hyperlipidemia	
Yes	4 (19%)
No	10 (47.6%)
Smoking	
Yes	7 (33.3%)
No	8 (38.1%)
Coronary artery disease	
Yes	7 (33.3%)
No	7 (33.3%)

SD: Standard deviation, min: Minimum, max: Maximum.

* The mean and standard deviation for the time of symptom-injection was calculated without including two patients who underwent off-label thrombolytic treatment eight and 12 hours after the onset of symptoms.

** Data from other risk factors, except atrial fibrillation, were not obtained from all patients, so the total number of patients with and without risk factors was not 21.

ITT was given to two patients even though the first 4.5 hours had passed. One of these patients was a 55-year-old male (patient 16). Diffusion-weighted MRI showed left paramedian pons infarction in the patient who was admitted with right 4/5 hemiparesis and moderate dysarthria nine hours after the onset of symptoms. Twelve hours after the onset of symptoms, the patient developed impairment in wakefulness, anarthria, and tetraparesis, predominantly on the right side. Repeated diffusion MRI showed no new infarction, and the basilar artery could not be seen in MR angiography. No center for endovascular treatment was found. Despite having a severe clinical picture suggesting basilar artery occlusion, no new lesions or enlargement of the previous lesion were detected in repeated diffusion-weighted MRI and the volume of the present lesion was small; ITT was given 12 hours after the onset of symptoms. Partial clinical improvement was observed in the patient and the NIHSS score was calculated as 8 just before the initiation of ITT. Even so, ITT was given. No complications were observed. The next morning, the NIHSS score was calculated as 5 and the patient was referred to the University Hospital for digital subtraction angiography (DSA). No angiography was performed in the patient and a follow-up decision was made with dual anti-aggregant treatment. The patient was able to walk with a single aid at the first month of follow-up (NIHSS 2). A week after this examination, the patient was admitted with an inability to walk. Diffusion-weighted MRI showed acute infarctions in the left posterior cerebral artery (PCA) territory and the right paramedian pons; the patient was referred to the University Hospital. It was learnt that during DSA, dissection in the basilar artery developed and the patient died three days later. The second patient (patient 10) who was treated with ITT beyond 4.5 hours was a 78-year-old female who was admitted to the emergency room with global aphasia, Vulpian sign, and right hemiplegia, 7.5 hours after the onset of symptoms. Diffusion-weighted MRI was normal and repeated MRI showed no lesion. Cranial CT angiography revealed right middle cerebral artery (MCA) M1 occlusion. No center for endovascular treatment was found. ITT was given to the patient, eight hours after the onset of symptoms. No bleeding occured in the patient but also no improvement in the clinical status happened and control cranial CT at 20 hours showed hypodens lesions in the right deep MCA and right cortical PCA territories. The patient died of pneumonia in the ICU two months later.

Intracerebral hemorrhage was observed in two (9.5%) patients after ITT. One patient (patient 5) was asymptomatic and was considered as hemorrhagic infarction type 1 according to the classification of the ECASS 2 trial. The second was symptomatic and was considered as parenchymal hematoma according to the ECASS 2 classification. The patient died despite undergoing decompressive surgery. This patient was a 65-year-old male (patient 21). He presented with global aphasia, right hemiplegia, and right homonymous hemianopsia, and the NIHSS score was calculated as 19; ITT was given at four hours after symptom-onset. IV esmolol was initiated in the appropriate dose for weight. The dose was increased because the arterial blood pressure exceeded 185/110 mmHg and rose above the defined limits. Generally blood pressure was kept below 180/105 mmHg but sometimes it rose above the defined limits. The patient did not benefit from the treatment and deteriorated 20 hours after ITT; therefore, he was sent for cranial CT, which revealed hemorrhage in the left deep

and cortical MCA territory causing a 1-cm midline shift. Due to the lack of cryoprecipitate in the hospital, fresh frozen plasma and thrombocyte suspension were given and then decompression surgery was performed but the patient did not benefit from surgery and died of pneumonia 1.5 months later in the ICU.

Cranial CT scans were performed in all patients and diffusion MRI was performed in 10 patients at the beginning. In our hospital, patients admitted to the emergency room with acute stroke are evaluated by an emergency medicine specialist and after brain imaging, they are referred to a neurologist. Accordingly, approximately half of the patients underwent both brain CT and diffusion-weighted MRI.

When patients with mRS scores 0-2 were accepted as having good outcome and patients with mRS scores 3-6 were accepted as having poor outcome, patients with NIHSS scores >14 had poorer outcomes compared with those with NIHSS scores ≤14 (p=0.007). In patients aged ≥80 years, there was a tendency for worse outcomes, although it was not statistically significant (p=0.17). The ratio of patients with NIHSS scores >14 among those aged ≥80 years was significantly higher compared with patients aged <80 years (p=0.041) (not shown in the table). There was no relation between sex, duration longer or shorter than three hours between the onset of symptoms and the onset of ITT, etiology, risk factors, and outcomes. No statistical analysis could be performed regarding bleeding complications because there were only two patients who developed intracerebral hemorrhage after ITT (Table 3).

Ten patients died in the three-month follow-up period, the mortality rate was calculated as 47.6%. The mRS score was 0-2 in eight (38.1%) patients and 0-1 in seven (33.3%) patients. ITT was given as off-label to five patients aged ≥80 years, five patients with NIHSS scores <5, and two patients who were outside the 4.5-hours treatment window.

Discussion

According to our findings, NIHSS scores >14 were related with poor outcomes (p=0.007). In patients aged ≥80 years, there was a tendency for worse outcome, although it was not statistically significant. Two patients developed intracerebral hemorrhage and one was symptomatic (4.75%), resulting in mortality. The mRS score was 0-2 in eight (38.1%) patients and 0-1 in seven (33.3%) patients. These findings show that ITT is safe and effective, and

Table 2. Clinical and demographic features and outcomes of the patients who were treated with intravenous thrombolytic therapy

No	Age	Sex	Etiology	Onset of symptoms-onset of treatment (minute)	NIHSS0	NIHSS24	mRS-pre-stroke	mRS at discharge or at 1 week	mRS at 3 months	Complications
1	84	F	U	270	18	18	0	6		None
2	82	F	LVD	270	21	21	0	6		None
3	52	F	CE	165	21	15	0	4	6	None
4	85	F	CE	225	17	17	0	5	6	None
5	85	M	CE	180	6	3	0	2	6	HI 1
6	86	F	SVD	180	4	4	0	1	0	None
7	73	F	U	240	4	17	0	6		None
8	68	F	U	210	9	0	3	3	2	None
9	48	M	U	150	12	10	0	4	3	None
10	78	F	CE	480	24	24	0	6		None
11	70	M	CE	240	8	2	0	1	0	None
12	71	M	LVD	120	2	2	0	0	0	None
13	79	F	CE	195	4	3	1	1	1	None
14	87	F	CE	150	15	15	3	5	6	None
15	75	M	LVD	170	4	2	0	3	0	None
16	55	M	LVD	720	8	8	0	3	6	None
17	80	F	CE	90	17	15	0	5	5	None
18	70	M	LVD	240	11	1	0	1	5	None
19	58	F	SVD	210	7	7	0	3	1	None
20	65	M	U	120	19	25	2	6		PH 2
21	62	M	CE	90	14	3	0	2	1	None

F: Female, M: Male, LVD: Large vessel disease, CE: Cardioembolic, SVD: Small vessel disease, U: Unknown, NIHSS: National Institutes of Health Stroke Scale, NIHSS0: NIHSS score before thrombolytic treatment, NIHSS24: NIHSS score 24 hours after thrombolytic treatment, HI 1: Hemorrhagic infartion type 1, PH 2: Parenchymal hemorrhage type 2, mRS: modified Rankin scale

Table 3. The comparison of demographic, clinical features, risk factors, and outcome of the patients

	Good outcome (mRS=0-2)	Poor outcome (mRS=3-6)	p
Age			
<80	7	7	0.17
≥80	1	6	
Sex			
Male	4	5	0.67
Female	4	8	
Symptom-treatment time			
0-3 hours	6	6	1.0
3-4.5 hours	4	7	
NIHSS score			
≤14	8	5	**0.007**
>14	0	8	
Etiology			
Large vessel disease	2	3	0.26
Cardioembolic	3	6	
Small vessel disease	2	0	
Unknown	1	4	
Risk factors*			
Atrial fibrillation			
Yes	2	6	0.4
No	6	7	
Hypertension			
Yes	6	6	1
No	2	1	
Hyperlipidemia			
Yes	1	3	0.24
No	7	3	
Diabetes mellitus			
Yes	2	3	0.6
No	6	4	
Smoking			
Yes	2	5	0.13
No	6	2	
Coronary artery disease			
Yes	5	2	0.6
No	3	2	

NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin scale.
*Data from other risk factors, except atrial fibrillation, were not obtained from all patients, so the total number of patients with and without risk factors was not 21.

that this study is a good example that demonstrates the necessity of ITT. We think that ITT can be applied in many centers in Turkey.

After the discovery of the recombinant form of tissue plasminogen activator (alteplase), a phase 3 randomized controlled study sponsored by the National Institute of Neurological Disorders and Stroke in 1995 showed that the use of alteplase within the first three hours of AIS was effective and safe (8). In 1996, the FDA licensed the use of alteplase in AIS. The ECASS trial, a phase 3 randomized controlled trial, showed the efficacy and reliability of ITT in AIS in 3-4.5 hours after the onset of symptoms (9). According to the current situation, alteplase is licensed in Europe for the first 4.5 hours and in the United States of America (USA), Canada, Croatia, and Moldova for the first three hours (10).

Apart from the aforementioned clinical studies, the Safe Implementation of Treatment in Stroke European trials aimed at investigating the outcomes of patients who were treated with ITT in daily practice. It was found that 40-45% of patients had mRS ≤1 and 55-60% of patients had mRS ≤2 at three months of ITT. The symptomatic intracranial hemorrhage rate was 2-7% and the mortality rate at three months was 12% (11,12). We found that 33.3% of patients had mRS ≤1 and 38.1% of the patients had mRS ≤2 at three months of ITT. The symptomatic intracranial hemorrhage rate was 4.75% and the mortality rate at three months was 47.6% in our study. The mRS ≤1 rate at three months and symptomatic intracranial hemorrhage rate were similar to those in the literature. The higher mortality rate and lower mRS ≤2 rate in our study could be explained by the higher rate of patients aged ≥80 years (33.3%) and significantly higher rate of NIHSS >14 among patients aged ≥80 years compared with patients aged <80 years (p=0.041). In addition, patients aged ≥80 years accounted for 23.8% of overall mortality rate (47.6%). Patients aged ≥80 years were shown to have lower mRS scores ≤2 (29%) at three months, but also it was highlighted that the size of the effect of ITT against placebo (19%) in patients aged ≥80 years was similarly high compared with the size of the effect of ITT in patients aged <80 years in the literature (13).

The mean time between the onset of clinical symptoms and initiation of ITT in developed countries was 140 minutes (12). This time was 184±53 minutes (patients who were treated with ITT at 8 and 12 hours after the beginning of symptoms were excluded from this calculation). In the literature, it is suggested that treatment should be started within 60 minutes after reaching the hospital (12). Unfortunately, these data were not recorded in our study, but we estimate that it took longer than 60 minutes.

Although ITT is the first-line treatment in AIS, it was reported that ITT had been performed in only 64 (30%) of 214 countries and independent regions in the world. According to this study, the income distribution of countries affected the rates of implementation of ITT. It was performed in 3% of low-income countries (1/36), and in 50% of high-income countries (35/75). According to the table in that study, Turkey was one of the countries with upper-intermediate income. Although ITT is performed, the complexity in the evaluation of the indications and of the clinical, radiologic, and laboratory contraindications of ITT in AIS and short therapeutic window limit its use. For example, ITT was administered to only 3.5% of all cases admitted in the USA in 2008 (14). It was reported that 25% of patients who were

admitted in 2 hours and had no contraindication for ITT did not receive ITT. The withdrawal rate of ITT decreased from 55% between 2003-2005 to 18% in 2010-2011 (15). Although we do not clearly know the situation in Turkey, it is estimated that the rate of implementation of ITT is increasing (5).

In the 2008/2009 AIS guideline update, the European Stroke Organisation recommended that ITT should be applied to patients over the age of 80 years and to patients in whom 3-4.5 hours have passed from the onset of symptoms (16,17), but still no license changes have been made. There are many contraindications in the license of alteplase that do not rely on scientific foundations and prevent the use of alteplase. According to a study, the percentage of non-compliance with the license after this update increased from 23.6% to 51%. For the indications, the rate of non-compliance increased from 8.2% to 27.9% in patients in whom more than 3 hours passed from the onset of symptoms, and increased from 8.9% to 17.2% in patients over the age of 80 years. For the contraindications, the rates of license non-compliance increased in patients with NIHSS >25, more than 4.5 hours after the onset of symptoms, arterial blood pressure higher than 185/110 mmHg, and in those using oral anticoagulants (18). In another study, 51% of patients who received ITT were shown to have one or more contraindications. These contraindications were as follows in order of frequency: age >80 years, NIHSS <5, IV antihypertensive need before treatment, symptom-needle time >3 hours, arterial blood pressure >185/110 mmHg, and oral anticoagulant use. Multivariate analysis showed that being aged over 80 years alone was associated with poor outcomes and none of the contraindications increased the risk of symptomatic intracranial hemorrhage. As a result, it was emphasized that off-label implementation of ITT was not associated with poor outcomes, except for age >80 years, and that licensing information should be rearranged in view of the results of studies (19). The AIS guideline published in 2018 no longer contains relative contraindications. A number of problems, other than indications and contraindications, has been identified in the "additional recommendations" section, which has allowed ITT to be given to many patients (20).

In our study, there were patients who were treated with ITT and who did not comply with the indications and/or contraindications of alteplase written in its license. Seven patients were aged ≥80 years, the NIHSS score was 2 in one patient and 4 in four patients, and 2 patients were given ITT outside the 4.5 hours treatment window. There was no increased risk of poor outcome or symptomatic hemorrhage in these patients, but the tendency to have poorer outcome in those aged ≥80 years was higher (p=0.17). It is important to note that outcome is good in patients with NIHSS <5, but can be better if ITT is given (21), and that 30% of patients discharged from the hospital could not walk without aid unless they received ITT (22).

Two patients in our study were treated with ITT more than 4.5 hours from the onset of symptoms. For this controversial implementation, we searched the literature. A Cochrane analysis published a year ago showed that the efficacy of ITT decreased after the first 3 hours, but mortality and disability rates were still decreased with ITT given up to 6 hours (23), and that new studies were needed to determine the limits of the treatment window. In the MR WITNESS study, patients with AIS in whom the time of symptom onset was not known and a mean of 4.5-24 hours passed after the latest healthy appearance were included and ITT was given safely to selected patients within 4.5 hours after the symptoms were noticed and quantitative MRI diffusion-fluid-attenuated inversion recovery mismatch was performed, and positive results were obtained (24). Another study based on the MRI diffusion-perfusion mismatch method in the same patient group is still ongoing (10). Although it was not an ITT study, according to the recent results of the DAWN trial, patients with AIS in whom a mean of 4.5-24 hours had passed after the latest healthy appearance and who had a mismatch between clinical status and diffusion MRI or perfusion CT had better outcomes if mechanical thrombectomy was performed compared with the control group (25). If we return to our patients, ITT was given to patient 10, 8 hours after the onset of symptoms due to negative results in 2 repeated diffusion MRIs, despite the patient having a severe clinical status and M1 occlusion was detected in CT angiography. ITT was given to patient 16, 12 hours after the onset of symptoms because the clinical status evolved from hemiparesis compatible with paramedian pons infarction seen in diffusion MRI, to a clinical picture including anarthria, loss of consciousness, and tetraparesis, which suggested the impairment of whole brain stem. The basilar artery was not seen in MR angiography and there was no new lesion in control diffusion MRI. In these two patients, ITT was decided to be administered with criteria similar to the diffusion MRI-clinical mismatch criteria in the DAWN trial. Although the results of the DAWN trial suggested that ITT might be beneficial in selected patients with mismatch between clinical status and infarction volume, the positive results of the DAWN trial could not be reflected in ITT use beyond 4.5 hours of the onset of symptoms, according to the present data (26). In addition, in a retrospective study of 14 patients with basilar artery thrombosis, low-dose ITT (≤20 mg) was given for 24 hours (minimum 10, maximum 48 hours). In 57% of patients, a decrease in thrombus size or no thrombus at all was detected on follow-up imaging and 64% were discharged with mRS scores 0-2 (27). However, there is no such practice in the current guidelines. Finally, we want to highlight that in the AIS guideline published in 2018, ITT was contraindicated in patients with more than 4.5 hours after the onset of symptoms, and in patients in whom the time of onset of symptoms was not known. We would like to emphasize that giving ITT in these two patients is not yet scientifically proven and should be avoided (20). Two important papers about ITT indications and contraindications have recently been published in the Turkish Journal of Neurology by the Turkish Society of Neurology (26,28).

Conclusion

The results of our study underscore the fact that ITT is effective and safe in the treatment of AIS and we encourage our colleagues throughout Turkey to give ITT.

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Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Mehmet Akif Inan Training and Research Hospital (protocol number: 64106871-090.99, date: 04.08.2017).

Informed Consent: Informed consent was taken from the patients or their relatives before the treatment was given.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.M.A., A.C.K., M.Ç.A., M.B., F.M., Concept: M.M.A., Ö.K., E.K., Design: M.M.A., Ö.K., A.Ö., M.B., Data Collection or Processing: M.M.A., M.Ç.A., A.C.K., Analysis or interpretation: M.M.A., Ö.K., F.M., E.K., Literature Search: M.M.A., M.Ç.A., A.Ö., M.B., Writing: M.M.A.

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