Turkish Journal of Cerebrovascular Diseases 2021; 27(2): 139-144 Türk Beyin Damar Hastalıkları Dergisi 2021; 27(2): 139-144
Turk J Cereb Vasc Dis
doi: 10.5505/tbdhd.2021.24993

RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

INTRAVENOUS THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE:

A STATE HOSPITAL EXPERIENCE, ANALYSES OF 87 CASES

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ABSTRACT

INTRODUCTION: Stroke is an acute dysfunction of the central nervous system. Treatment of ischemic stroke in the acute period is very important. Intravenous thrombolytic therapy with recombinant tissue plasminogen activator is one of the most important reperfusion strategies. The aim of this study is to evaluate the data of patients who have been diagnosed with acute ischemic stroke and treated with IV tPA in a state hospital.
METHODS: Patients who were admitted with acute ischemic stroke and treated with IV tPA between June 2017 and June 2020 at Burdur State Hospital Neurology Clinic were evaluated retrospectively. Patients who met the criteria and who could be treated within 4.5 hours from the onset of symptoms were included. Demographic features, clinical data, NIHSS scores before and after treatment, symptom onset time, hospital admission time and treatment start time were recorded.
RESULTS: 87 patients (41 men (47,1%), 46 women (52,9%)) with a mean age of 67.5±12.1 were included in the study. The mean symptom-door, door-needle and symptom-needle time of the patients were 76.4±35.7, 59.1±34.9 and 135.5±38.1, respectively. The mean NIHSS score of the patients was 11.8±3.9 at admission and 5.2±2.6 at the 24th hour after treatment. The mean NIHSS score was found to be 3.5±2.9 during discharge. Pre- and post-treatment NIHSS score, symptom-door time and door-needle time were compared between survivor and non-survivor patients. Significantly lower scores and shorter times were found in survivor patients ($p<0.001$).
DISCUSSION AND CONCLUSION: IV tPA is an effective and safe treatment under appropriate conditions in patients with acute ischemic stroke. State hospitals will be an important center for thrombolytic therapy with public and in-hospital organizations to be made about effective use of time.
Keywords: White matter lesions, dementia, cognition, small vessel disease, lacunar infarct, Mini Mental State Examination, vascular lesions.

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Received: 10.02.2021 **Accepted:** 16.03.2021
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Please cite this article as following: Ongun N. Intravenous thrombolytic therapy in acute ischemic stroke: A state hospital experience, analyses of 87 cases. Turkish Journal of Cerebrovascular Diseases 2021; 27(2): 139-144. doi: 10.5505/tbdhd.2021.24993

AKUT İSKEMİK İNMEDE İNTRAVENÖZ TROMBOLİTİK TEDAVİ:

BİR DEVLET HASTANESİ DENEYİMİ, 87 OLGU ANALİZİ

ÖZ

GİRİŞ ve AMAÇ: İnme, santral sinir sisteminin akut bir disfonksiyonudur. İskemik inmenin akut dönemde tedavisi büyük önem taşımaktadır. Rekombinant doku plazminojen aktivatörü ile intravenöz trombolitik tedavi, en önemli reperfüzyon stratejilerinden birisidir. Bu çalışmanın amacı, bir devlet hastanesinde akut iskemik inme tanısı ile IV tPA tedavisi uygulanan hastaların verilerinin değerlendirilmesidir.

YÖNTEM ve GEREÇLER: Burdur Devlet Hastanesi Nöroloji Kliniği'nde Haziran 2017 - Haziran 2020 tarihleri arasında akut iskemik inme tanısı ile intravenöz trombolitik tedavi uygulanan hastalar geriye dönük olarak değerlendirildi. Kriterlere uyan ve semptom başlangıcından itibaren 4,5 saat içerisinde tedavi uygulanabilecek olan hastalara tPA uygulandı. Hastaların demografik özellikleri, klinik verileri, tedavi öncesi ve sonrası NIHSS skorları, semptom başlangıç zamanı, hastane başvuru zamanı ve tedavi başlangıç zamanı kayıt edildi.

BULGULAR: Çalışmaya yaş ortalaması 67.5±12.1 olan 87 hasta (41 erkek (%47,1), 46 kadın (%52,9)) alındı. Hastaların ortalama semptom-kapı, kapı-iğne ve semptom-iğne zamanları dakika olarak sırası ile 76.4±35.7, 59.1±34.9 ve 135.5±38.1 olarak saptandı. Hastaların NIHSS skoru ortalaması başvuru sırasında 11.8±3.9, tedavi sonrası 24. saatte 5.2±2.6 olarak bulundu. Taburcu olan hastaların taburculuk sırasında NIHSS skoru ortalaması 3.5±2.9 olarak bulundu. Taburcu olan ve kaybedilen hastalar, tedavi öncesi NIHSS skoru, tedavi sonrası 24. saat NIHSS skoru, semptom-kapı zamanı ve kapı-iğne zamanı açısından karşılaştırıldığında, taburcu olan hastalarda anlamlı olarak daha düşük skorlar ve daha kısa zamanlar saptandı ($p<0.001$).

TARTIŞMA ve SONUÇ: Akut iskemik inme nedeni ile değerlendirilen hastalarda uygun şartlar altında IV tPA etkili ve güvenilir bir tedavidir. Zamanı etkin kullanmaya yönelik yapılacak olan toplumsal ve hastane içi organizasyonlar ile devlet hastaneleri trombolitik tedavi için önemli birer ilk başvuru merkezi olacaklardır.

Anahtar Sözcükler: Akut iskemik inme, trombolitik tedavi, devlet hastanesi.

INTRODUCTION

Stroke is an 80% ischemia condition characterized by an acute dysfunction of the central nervous system (1). While stroke is the third biggest cause of mortality in many countries, after cardiovascular disease and cancer, it is also the leading cause of disability in adults (2).

The penumbra tissue, where permanent damage has not yet occurred owing to collateral circulation, is the focus in the therapy of ischemic stroke. Therefore, the treatment of stroke in the acute period is of great importance. Thrombolysis with intravenous (IV) recombinant tissue plasminogen activator (tPA) is one of the most beneficial reperfusion strategies (3).

Since 2006, when the IV tPA medication was licensed in our country, its use has grown in popularity. The therapy has started to be administered efficiently at secondary health institutions where the highest number of patient applications are received, thanks to increased awareness and the number of experienced physicians. The purpose of this study is to examine the data of patients who received IV tPA therapy at a state hospital for acute ischemic stroke.

MATERIALS AND METHODS

Patients who received intravenous thrombolytic treatment for acute ischemic stroke at Burdur State Hospital's Neurology Clinic between June 2017 and June 2020 were studied retrospectively.

All patients were assessed based on the inclusion and exclusion criteria established by the Turkish Neurological Society Cerebrovascular Diseases study group. The patients' demographic characteristics, clinical data, pre- and post-treatment National Institutes of Health Stroke Scale (NIHSS) scores, symptom onset time, hospital admission time, and treatment start time were all recorded.

After obtaining their informed consent, patients who could be treated within 4.5 hours of symptom onset were given tPA at a dosage of 0.9 mg/kg (maximum 90 mg, 10% of total estimated dose as an IV bolus, remainder dose as an IV infusion in one hour).

SPSS 21.0 was used for statistical analysis (IBM, Chicago, IL, USA). Basic statistical analysis was performed using descriptive statistics tables.

Continuous variables were expressed as

mean±standard deviation, and categorical data as median and percentage. The t-test was applied to compare pre-treatment and post-treatment NIHSS scores.

The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee (Date: 06.03.2018 Number: 05), and it was carried out in line with the ethical standards of the Declaration of Helsinki.

RESULTS

The study comprised 87 patients (41 males (47.1%), 46 females (52.9%)) with a mean age of 67.5±12.1 years. Demographic characteristics of the patients are presented in Table 1.

Table 1. Demographic characteristics of patients.

Characteristic	n=87
Age (mean ± SD , year)	67.5 ± 12.1
Gender (n, %)	
Male	41 (47,1)
Female	46 (52,9)
Marital Status (n, %)	
Married	55 (63,2)
Single	8 (9,2)
Divorced/Widowed	24 (27,6)
Educational Status (n, %)	
Illiterate	19 (21,9)
Primary school	28 (32,2)
Middle School	22 (25,2)
High School	12 (13,9)
University	6 (6,8)

The most common risk factors were discovered to be hypertension (40 patients, 45.9%), smoking (33 patients, 37.9%), and hyperlipidemia (26 patients, 29.8%) (Table 2). 76 patients (87.4%) were evaluated in the emergency department, 9 patients (10.3%) in the neurology outpatient clinic, and 2 patients (2.3%) were in other clinics and given IV tPA (Table 2). The mean time from symptom onset to hospital admission (Symptom-Door time), the mean time from hospital admission to treatment initiation (Door-Needle time), and the mean time from symptom onset to treatment initiation (Symptom-Needle time) were found to be 76.4±35.7, 59.1±34.9, and 135.5±38.1 minutes, respectively (Table 2).

The mean NIHSS score of the patients was found to be 11.8±3.9 at admission and 5.2±2.6 at the 24th hour after treatment. The mean NIHSS score of the released patients was 3.5±2.9 at the time of discharge.

When the pre-treatment NIHSS score, the 24th-hour post-treatment NIHSS score, the symptom-door time, and the door-needle time of discharged and deceased patients were compared, discharged patients were found to have significantly lower scores and shorter times ($p<0.001$) (Table 3).

After the treatment, intracranial hemorrhage was discovered in 10 patients (11.4%). Six individuals (6.8%) experienced symptomatic hemorrhage, and four of these patients died. It was observed that all patients with symptomatic bleeding had an NIHSS score of 18 and above at the time of admission.

Table 2. Clinical characteristics of patients.

Characteristic	n=87
Risk Factors (n, %)	
Hypertension	40 (45,9)
Diabetes Mellitus	16 (18,3)
Atrial Fibrillation	21 (24,1)
Coronary Artery Disease	17 (19,5)
Hyperlipidemia	26 (29,8)
Smoking	33 (37,9)
Hospitalization (n, %)	
Emergency Department	76 (87,4)
Policlinic	9 (10,3)
Inpatient	2 (2,3)
Symptom-Door Time (mean±SD, min.)	76.4±35.7
Door-Needle Time (mean±SD, min.)	59.1±34.9
Symptom–Needle time (mean±SD, min.)	135.5±38.1

Table 3. Comparison of discharged and deceased patients in terms of NIHSS, symptom-door and door-needle times.

	Discharged Patients (n=71) (mean ± SD)	Deceased Patients (n=16) (mean ± SD)	P-Value
Pre-Treatment NIHSS	10.5±3.6	17.4±5.1	<0.001
24th-Hour Post-Treatment NIHSS	3.5±2.9	12.7±4.9	<0.001
Symptom-Door Time (min.)	69.7±32.4	105.8±39.9	<0.001
Door-Needle Time (min.)	52.4±27.9	88.7±34.7	<0.001

DISCUSSION AND CONCLUSION

In our retrospective study of our patients who underwent IV thrombolytic treatment with the diagnosis of acute ischemic stroke, the most prevalent risk factors in our patients were hypertension, smoking, and hyperlipidemia. 87.4% of the patients were assessed in the emergency department and treated. Treatment was initiated approximately 59.1 minutes after being admitted to the hospital. It was observed that the survival rate was higher in patients with low stroke scores and short hospital admission and treatment initiation times.

Even though the benefits of IV tPA in the treatment of acute ischemic stroke are recognized worldwide, it is still not frequently employed. Studies conducted in the United Kingdom and USA have revealed that the therapy is not employed in the vast majority of patients who have a chance to benefit from IV tPA treatment due to stroke (4,5). Patients should be examined immediately in appropriate centers in order to plan efficient therapy for stroke patients. Although the number of studies conducted in our country is progressively rising, data from secondary level state hospitals with the largest number of patient applications is limited. In this regard, our study is significant in terms of contributing to the literature.

The duration of IV tPA administration is recommended as 4.5 hours in the treatment of acute ischemic stroke (6,7). Up to the time of reperfusion, roughly 2 million neurons and 14 billion synapses are lost per minute (8). In a study of patients who had tPA, it was reported that giving the therapy 15 minutes before the procedure reduced mortality and intracranial hemorrhage rates and improved overall well-being after discharge (9). Therefore, it is vital to initiate the treatment as soon as possible from the onset of symptoms. The reason for the low rate of IV tPA use in secondary state hospitals is the difficulties experienced in the organizations of the stroke unit/center operating 24/7 and the ineffective use of time, which is the most crucial criterion for treatment. The time elapsed between the start of symptoms and the delivery of IV tPA therapy has been demonstrated to be the most significant factor determining the efficacy of the treatment (10). All patients included in our study were treated within the first 4.5 hours from the onset of acute ischemic stroke symptoms. The mean symptom-door (S-D) time was 76.4 minutes, and the mean door-needle (D-N) time was 59.1 minutes. The S-D duration was determined to be 81 minutes and the D-N time to be 69.5 minutes in a multicenter study conducted in our country by the Turkish National Intravenous Thrombolysis Study Group (11). In other studies conducted in our country, S-D and D-N times were found to be 70-85 minutes, 72-74 minutes, and 76-72 minutes, respectively (12- 14). The S-D time we obtained in our study was similar to the findings in other studies. On the other hand, our D-N time was found to be shorter than the times obtained in other studies. Patients' admission to the hospital as soon as possible following the onset of symptoms is considered directly related to the level of consciousness and awareness on this issue. In this regard, we believe that the public education sessions we host and the training we organize for emergency health care personnel, who are the first line of defense for patients, are critical. The fact that we were the only hospital in Burdur's city center where we conducted the study positively influenced the S-D time. The majority of treated patients were assessed in the emergency department in our study, as in other studies. We believe the D-N time results we obtained are attributable to the periodic training offered to all hospital personnel, particularly in the emergency department, and to the structured follow-up of the patient throughout the process until imaging and subsequently treatment.

Symptomatic intracranial hemorrhage (with an increase in NIHSS score of 4 or more) is the most feared complication of IV tPA treatment, with a mortality rate of about 50% (15). Hemorrhaging within the first 36 hours is associated with thrombolytic therapy. In studies with large series, this rate was found to be 6.4%, 2.4%, and 7%, respectively (16-18). However, in studies conducted in our country, these rates were discovered to be as high as 16%, 3.8%, and 15% (13,14,12). The rate of symptomatic intracranial hemorrhage was found to be 6.8% in our study. Similar to the cases reported in the literature, it was observed that the risk of hemorrhage after treatment was higher in patients with relatively longer door-needle times and higher NIHSS scores. Hemorrhagic transformation rates following IV

tPA were previously reported to be 17% and 3%, respectively, with NIHSS≥20 and <10 (19).

Similarly, all the patients with symptomatic hemorrhage in our study had an admission NIHSS score of 18 or above.

A statistically significant difference was found between discharged patients and deceased patients in terms of pre-treatment NIHSS score, 24th-hour post-treatment NIHSS score, S-D time, and D-N time. Similarly, in other studies conducted in our country, it has been shown that discharged patients have lower "pre- and post-treatment NIHSS scores" and symptom-needle times (13,14). A pooled analysis of multicenter studies showed that those who started treatment earlier in the time range had a better probability of recovery (20). The NIHSS is the most widely used scale for evaluating clinical findings. The severer the clinical picture is, the higher the NIHSS score is. Patients with moderate-to-severe deficits are considered the target population for IV tPA, or the group with the best benefit-risk ratio, with an NIHSS score of 6 to 22 (21). Treatment-related complication rates increase as the NIHSS score rises and treatment benefit rates decrease. The treatment benefit rate is greater in patients with shorter S-D and D-N times. This condition emphasizes the necessity of education of people at all stages of the diagnostic and treatment process. People at all levels, including the general public, ambulance service employees, emergency physician and assistant health care staff, and imaging service workers, must act promptly and conscientiously.

In conclusion, IV tPA is an effective and safe therapy for patients with acute ischemic stroke when used under the right circumstances. State hospitals will be an essential initial application center for thrombolytic therapy, with social and in-hospital organizations to be established for using time effectively.

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Ethics

Ethics Committee Approval: The study was approved by Pamukkale University Noninterventional Clinical Ethical Committee (Number: 05, Date: 06.03.2018).

Informed Consent: The author declared that it was not considered necessary to get consent from the patients because the study was a retrospective observational study.

Copyright Transfer Form: Copyright Transfer Form was signed by the author.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: NO. Concept: NO. Design: NO. Data Collection or Processing: NO. Analysis or Interpretation: NO. Literature Search: NO. Writing: NO.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study received no financial support.