ORIGINAL ARTICLE

Characteristics of Patients Administrated Thrombolytics in the Emergency Department

Acil Serviste Trombolitik Uygulanan Hastaların Özellikleri

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ABSTRACT

Objective: Arterial and venous thromboembolism is one of the most prevalent diseases and related to ischemic stroke, pulmonary embolism, and myocardial infarction leading to mortality or is morbidity. Fibrinolytic therapy is the most profound lifesaving therapy in these diseases. We aimed to evaluate the demographic features and post-tissue plasminogen activator (tPA) period of patients administered fibrinolytic in the emergency department (ED).

Materials and Methods: This retrospective study was conducted with patients instituted fibrinolytic therapy in the ED between January 2018 and July 2021. Age and gender of the patients, vital signs, laboratory tests, comorbidities, drugs used, lifesaving therapies secondary to the present pathology, tPA complications, mortality and similar presentations within the six months period were recorded to the study form.

Results: A total of 277 patients were included in the study. Ischemic stroke was the most prevalent disease entailing the institution of tPA (n=252; 91%). The study patients mostly used antihypertensives (n=155, 56%), followed by anti-aggregants (n=101, 36.5%). Intracranial hemorrhage (11.9%) was the most frequent complication secondary to tPA and the study patients had mostly undergone thrombectomy as a lifesaving therapy (n=34, 12.4%). The univariate analysis revealed that antiaggregant usage (n=21, 53.8% vs n=80, 33.6%; p=0.01), systolic blood pressure (160 mmHg, IQR: 138-190 vs 150 mmHg 130-169; p=0.02) and diastolic blood pressure (90 mmHg, IQR: 75-100 vs 83 mmHg, IQR: 72-94; p=0.03) differ between the patients with and without a post-tPA hemorrhage.

Conclusion: According to the results of this study, ischemic stroke is the main pathology related to tPA administration in ED. Hypertension was the most seen comorbidity in study patients, mostly using anti-hypertensive and anti-aggregants. Intracranial hemorrhage was the most prevalent complication owing to tPA use, and systolic and diastolic blood pressures and anti-aggregant use pertain to post-tPA hemorrhages.

Key Words: fibrinolytic therapy, stroke, pulmonary embolus, intracranial hemorrhage, complication, emergency department, thromboembolism

ÖZ

Amaç: Arteriyel veya venöz tromboembolizm günümüzde sık görülen hastalıklardan birisi olup; iskemik inme, pulmoner emboli ve miyokart infarktüsü gibi mortalite ve morbiditesi yüksek patolojiler ile ilişkilidir. Fibrinolitik tedavi bu hastalıklarda hayat kurtarıcı en önemli tedavidir. Bu çalışmada fibrinolitik tedavi almış hastaların demografik verileri ile takip süreçlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: 1 Ocak 2018 – 1 Temmuz 2021 tarihleri arasında acil servise başvuran ve fibrinolitik tedavi alan hastalar geriye dönük olarak bu çalışmaya dahil edildi. Çalışma hastalarının yaş, cinsiyet, fibrinolitik uygulama nedeni, vital bulguları, laboratuvar tetkikleri, ek hastalıkları, kullandığı ilaçlar, hastalığa yönelik aldığı ek tedaviler, tedavilerin komplikasyonları, mortalite ve 6 aylık süreçte benzer tanılı başvuruları kaydedildi.

Bulgular: Toplamda 277 hasta çalışmaya dahil edildi. Çalışmada acil serviste en sık tPA uygulama nedeni iskemik inmeydi (n=252; %91). tPA uygulanan hastalarda en sık görülen komplikasyon %11,9 ile intrakraniyal kanama, en sık uygulanan kurtarıcı tedavi ise trombektomiydi (n=34, %12,4). Hastaların en sık kullandığı ilaç %56 (n=155) ile anti-hipertansifler olup, anti-hipertansifleri %36,5 (n=101) ile anti-agreganlar, %30 (n=83) ile anti-diyabetikler, %24,5 (n=68) ile anti-aritmik ilaçlar takip etmekteydi. Yapılan tek değişkenli analizde, tPA uygulaması sonrası kanama meydana gelen ve gelmeyen hastalar arasında anti-agregan kullanımı (n=21, %53,8 vs n=80, %33,6; p=0,01), sistolik kan basıncı (160 mmHg, IQR: 138-190 vs 150 mmHg 130-169; p=0,02) ve diyastolik kan basıncı (90 mmHg, IQR: 75-100 vs 83 mmHg, IQR: 72-94; p=0,03) açısından anlamlı fark vardı. Çok değişkenli analizde ise post-tPA kanama ile ilişkili bağımsız değişken olarak sadece anti-agregan kullanımı saptandı.

Sonuç: Bizim çalışmamızın sonuçlarına göre, acil servisimizde en sık tPA verilme endikasyonu iskemik inmedir. tPA verilen hastalarda en sık yandaş hastalık hipertansiyon olup, en sık kullanılan ilaç antihipertansifler ve antiagreganlardır. İntrakraniyal kanama tPA verilen hasta grubunda en sık görülen komplikasyon olup, sistolik ve diyastolik kan basıncı ile antiagregan kullanımı tPA kullanımı sonrası kanamalarla ilişkilidir.

Anahtar Kelimeler: fibrinolitik tedavi, inme, pulmoner emboli, intrakaniyal kanama, komplikasyon, acil servis, tromboembolizm

Introduction

Arterial and venous thromboembolism is one of the most frequently diagnosed disease groups. The development of diagnostic methods, studies on the epidemiology of this disease group, the distribution of diseases and diagnosis and treatment strategies are increasing and developing day by day. Thromboembolic disease is an important cause of mortality and morbidity in our country and in the world. Fibrinolytic therapy is one of the alternative treatment methods used in the first stage of the disease in thromboembolic diseases. It allows the thrombus to lysis without being organized in the vessel and to

continue the flow. Thrombolytics are used in the acute treatment of ischemic stroke, pulmonary embolism and myocardial infarction (4). Possible side effects are local or systemic bleeding and allergic reactions (5).

Emergency services are the first hospital unit where acute thromboembolic diseases are diagnosed and treated, and the treatment of patients starts in emergency services. Health providers are establishing stroke centers in the emergency departments for ischemic stroke and establishing special ambulance units. It would not be wrong to predict that emergency services will continue to be essential for thromboembolic diseases in the near future (6). Today, although there are many studies on thromboembolic diseases and fibrinolytic administration, there are not enough studies examining the data of our country.

In this study, we aimed to determine retrospectively the epidemiology and demographic data, possible complications and outcomes of patients who received fibrinolytic therapy in the emergency department due to thromboembolic events.

Materials and Methods

This study was carried out retrospectively on patients admitted to the Emergency Medicine Clinic of Health Sciences University Antalya Training and Research Hospital and received fibrinolytic therapy between January 1, 2018 and June 1, 2021, after the approval of the local ethics committee. Inclusion criteria for the study were that all patients received fibrinolytic therapy after admission to the emergency department, and the exclusion criteria were that the patient was younger than 18 years of age and the patient's data could not be accessed.

Tissue plasminogen activator (tPA) was used as fibrinolytic in our hospital and the patients to be included in the study were determined by learning the names and entry numbers of the patients who received tPA from the central pharmacy of the hospital. The names, ages, genders, diagnoses, vital signs, biochemical tests, comorbidities, drugs used, treatment dose received, complications due to the treatment received, additional treatments, and outcomes of the patients were recorded in the study form, in order. Finally, whether the patients were diagnosed with a similar disease in the 6th month after the treatment and their survival were checked over the operating system of our hospital.

Statistical Analysis

Study data were analyzed with SPSS (Statistical Package for the Social Sciences) 23.0 and MedCalc 20.110 programs. Numerical data were expressed as mean±standard deviation and interquartile range (IQR), and frequency data were expressed as percentages. Mann Whitney U test was used to compare two independent groups for numerical data, and Pearson Chi-square and Fischer's Exact tests

were used for frequency data. Normality analysis was performed with the Kolmogorov-Smirnov test. Logistic regression analysis was employed to determine the independent variable that can be used to determine bleeding after tPA application. All hypotheses were established in two ways and the alpha critical value was accepted as 0.05.

Results

Of the 301 patients who provided the inclusion criteria, 24 were excluded because their data could not be reached, so 277 patients were included in the final analysis (Figure 1). The mean age of the patients was 69±14.6. 54.5% (n=151) of the patients were male. The mean systolic blood pressure of the patients treated with fibrinolytics was 152±32 mmHg, and the diastolic blood pressure was 85±20 mmHg. The mean hospital stay of the patients included in the study was 10-16 days. The most common reason for tPA application in our emergency department was ischemic stroke (n=252; 91%), followed by pulmonary embolism (n=24; 8.7%) and myocardial infarction (n=1; 0.4%). The mean platelet value of the study patients was 245,000±84,000 units/dl, the creatinine value was 1.1±0.4 mg/dl, the glucose value was 145±70 mg/dl, and the median troponin value was 17 ng/ml (IQR: 8-32.5). The mean tPA dose administered to the patients was 64±18 mg. The general demographic data and laboratory values of the patients are given in Table 1.

In the univariate analysis, there was a significant difference in antiaggregant use (n=21, %53.8 vs n=80, %33.6; p=0.01), systolic blood pressure (160 mmHg, IQR: 138-190 vs 150 mmHg 130-169; p=0.02) and diastolic blood pressure (90 mmHg, IQR: 75-100 vs 83 mmHg, IQR: 72-94; p=0.03) between patients who had bleeding and did not have bleeding after tPA application. (Figure 2,3) (Table 3).
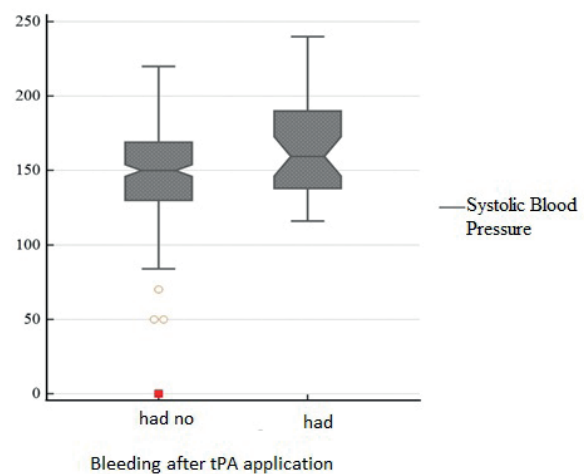

Figure 1. Box-and-whisker graph belongs to systolic blood pressure of patients with and without bleeding after tPA application
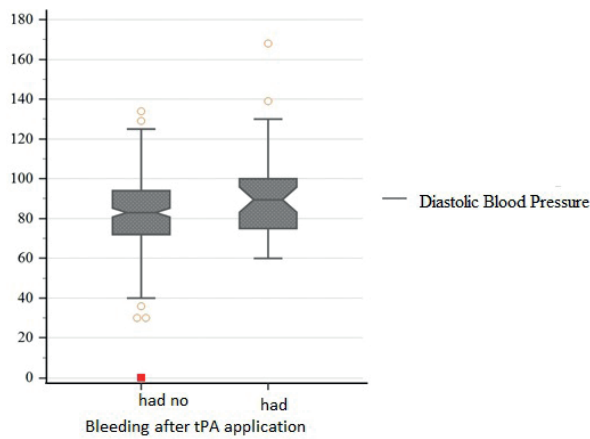
Figure 2. Box-and-whisker graph belongs to diastolic blood pressure of patients with and without bleeding after tPA application

Table 1. Demographic data and laboratory values of study patients

Variables	N (%)
Gender	
Female	126 (45.5)
Male	151 (54.5)
Diagnosis	
Ischemic Stroke	252 (91)
Pulmonary Embolism	24 (8.7)
Myocardial infarction	1 (0.4)
	mean±SD
Age	69±14.6
Systolic blood pressure	152±32
Diastolic blood pressure	85±20
Heart rate	92±25
Oxygen Saturation	95±5
Hospitalization (day)	10±16 6 (4-10.5)*
NIHSS (At the time of application)	9.5±4
Hemoglobin	12.4±2
Thrombocyte	245±84
INR	1±0.3
Creatinin	1.1±0.4
Alanine aminotransferase	26±89 15 (11-21)*
Aspartate Aminotransferase	33±94 21 (17-27)*
Glucose	145±70
Troponin	60±193 17 (8-32.5)*
D-dimer	4032±7735 1578 (652-3242)*
tPA Dosage	64±18

NIHSS: National Institutes of Health Stroke Scale; INR: International Normalized Ratio; tPA: Tissue Plasminogen Activator

Table 2. Co-morbidities and medications used by study patients

Variables	N (%)
Diabetes	93 (33.6)
Hypertension	156 (56.3)
Coronary Artery Disease	87 (31.4)
Heart Failure	41 (14.8)
Peptic Ulcer (Active)	15 (5.4)
Ischemic Stroke (Before 3 months)	46 (16.6)
Malignant (Except Intracranial mass)	13 (4.7)
Atrial Fibrillation	58 (20.9)
Antiaggregant Usage	101 (36.5)
Warfarin Usage	9 (3.2)
Antihypertansive Usage	155 (56)
Antidiabetic Usage	83 (30)
Antiarrhytmic Drug Usage	68 (24.5)
Other Drugs	134 (48.6)

Table 3. Comparison of patients with and without bleeding after tPA in terms of parameters such as age, vital signs and bleeding profile

Variable	Post-tPA Beleeding (+) Median (IQR)	Post-tPA Bleeding (-) Median (IQR)	P value
Age	70 (57-79)	71 (61-80)	0.98
Systolic Blood Pressure	160 (138-190)	150 (130-169)	0.02
DiastolicBlood Pressure	90 (75-100)	83 (72-94)	0.03
Diabetes	12 (30,8)	81 (34)	0.69
Hypertension	24 (61.5)	132 (55.5)	0.48
Peptic Ulcer	2 (5.1)	13 (5.5)	1
Malignant	2 (5.1)	11 (4.6)	1
Previous Ischemic Stroke (Before last 3 months)	7 (17.9)	39 (16.4)	0.80
Anti-aggregant Usage	21 (53.8)	80 (33.6)	0.01
Warfarin Usage	2 (1.3)	7 (2.9)	0.62
High INR	2 (5.1)	18 (7.6)	0.58
Diagnosis			
Stroke	38 (15.1)	214 ((84.9)	0.22
PE and MI	1 (4)	24 (96)	
Thrombocyte	223 (185-294)	238 (190-293)	0.79
INR	1 (1-1)	1 (1-1)	0.98
Creatinin	1 (1-1)	1 (1-1)	0.83
tPA Dosage	63 (54-73)	63 (50-78)	0.87
NIHSS	9 (6-12)	10 (7.5-12.5)	0.16

NIHSS: National Institutes of Health Stroke Scale; PE: Pulmonary embolism; MI: Myocardial infarction; INR: International Normalized Ratio; tPA: Tissue Plasminogen Activator

Discussion

This study showed that the most common cause of fibrinolytic administration in our emergency department was ischemic stroke. In their study, Arslan et al. reported that patients who received fibrinolytic therapy in the emergency department received treatment with the most common diagnosis of ischemic stroke (7). It can be said that this result is related to the frequency of diagnosis of ischemic stroke and pulmonary embolism in the emergency department and the indications for fibrinolytic administration of these two disease groups. According to the results of this study, the patients who underwent tPA were mostly male (54.5% n=151) and elderly (69±14.6) patients. In the study conducted by Emberson et al., 55% of stroke patients were male and the mean age was 71 (8). Since ischemic stroke patients constituted a significant part of this study, gender distribution and mean age were also compatible with the demographic profile of ischemic patients.

According to the results of the study, the most common comorbid disease in patients receiving tPA treatment is hypertension. In the study conducted by Kleindorfer et al., the most common co-morbid disease in patients receiving tPA treatment for ischemic stroke was hypertension (9). In the study of Anderson et al., the most common co-morbid disease in patients with ischemic stroke who received tPA treatment was hypertension, followed by diabetes and coronary artery disease (10). Hypertension is the most common comorbid disease in patients receiving tPA in the literature, which is consistent with the results of our study.

In our study, the most common complication in patients who received tPA treatment was intracranial bleeding, followed by other system bleeding and allergic reactions. In the studies conducted by Liu et al., Gilliland et al., and Vivien et al. in the literature, the most common complication was intracranial hemorrhage (11-13). The results of this study are compatible with other studies in the literature. The fragile nature of necrotic and ischemic brain tissue in ischemic stroke patients increases the frequency of bleeding in the intracranial area compared to other tissues without pathology. Variables associated with post-tPA bleeding in univariate analysis; and diastolic blood pressure, systolic blood pressure and antiaggregant use. In the study conducted by The NINDS t-PA Stroke Study Group, systolic and diastolic blood pressure were associated with post-tPA bleeding in univariate analysis (14). In the multivariate analysis performed by Tong et al. in 7193 ischemic stroke patients given tPA, age and NIHSS score were related to symptomatic intracranial hemorrhage (15). In their study, Tsivgoulis et al. found that violation of blood pressure protocols before treatment was associated with increased symptomatic intracranial bleeding in patients given tPA (16). In a multivariate analysis of 11080 ischemic stroke patients who underwent fibrinolysis, Ahmed et al. found a linear relationship between post-tPA 2-24 hour high blood pressure (as a categorical variable) and symptomatic bleeding (17). Berge et al. found that the blood pressure of patients with symptomatic intracranial hemorrhage in 3035 patients with ischemic stroke who received tPA was significantly higher than those without hemorrhage. However, multivariate analysis was not performed for other parameters that might affect bleeding (18). In the ENCHANTED study, where 2196 ischemic stroke patients eligible for tPA and two groups with a target blood pressure of 130-140 mmHg or <180 mmHg were compared, the frequency of any intracranial bleeding was significantly less in the group with intensive blood pressure control than in the other group (14.8% vs. 18.7%; p=0.01) (10). Although there are studies in the literature that found contrary findings, the majority of the studies found that increased blood pressure was associated with bleeding after tPA. In addition, providing blood pressure control in patients before tPA administration will also affect the results of studies that perform the analysis by accepting blood pressure as a continuous variable. In this study, the correlation of systolic and diastolic blood pressure with post-tPA bleeding in univariate analysis was consistent with the literature, but the same significance was not found in multivariate analysis.

In our study, in the multivariate analysis, only anti-aggregant use was found as the independent variable associated with post-tPA bleeding. Cucchiara et al. determined that antiaggregant use and NIHSS score were associated with symptomatic intracranial hemorrhage in multivariate analysis in patients with ischemic stroke who were given tPA in the first three hours (19). In the study of Larrue et al., it was reported that old age and ASA use in patients receiving thrombolytic therapy were related to bleeding after post-thrombolytic therapy (20). In the study conducted by The NINDS t-PA Stroke Study Group, no relationship was established between bleeding after tPA and the use of anti-aggregants (14). In the study of Tanne et al., antiplatelet agents other than aspirin were found to have been associated with symptomatic intracranial bleeding in multivariate analysis (21). The results of this study are generally compatible with the results of studies in the literature.

This study has many limitations. This study was planned retrospectively. This study was carried out in the emergency department of a tertiary hospital. There may be differences between the patient profile of a tertiary hospital and the patient profile of a lower level hospital. Similar studies to be conducted in different hospitals may provide better information about the demographic characteristics and follow-up processes of patients who received fibrinolytic therapy. Only patients given alteplase from the tPA drug group were analyzed in this study. It is not possible to make a clear comment regarding the possible side effects of other agents used for thrombolysis in the patient group evaluated in this study. Further studies are needed with

the use of other thrombolytic agents in the emergency department.

Result

According to the results of this study, the most common indication for tPA administration in our emergency department is ischemic stroke. The most common co-morbid disease in patients receiving tPA treatment is hypertension, and the most commonly used drugs are antihypertensives and antiaggregants. Intracranial bleeding is the most common complication in the patient group given tPA, and systolic and diastolic blood pressure and antiaggregant use are associated with bleeding after tPA.

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