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Original Article / Özgün Araştırma

5-Years of Thrombolytic Treatment Experience

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Abstract

Objective: Thrombolytic therapy has a vital role in saving both life and vital functions in emergency room patients. Our aim in our study is to reveal the thrombolytic practice experience of a 3rd level hospital in a long period of 5 years.

Methods: Adult patients who applied to the emergency department between 2017-2022 and were given thrombolytic therapy were selected. Demographic information, risk factors, laboratory and radiological parameters, diagnoses and thrombolytic use of the patients were examined.

Results: 56 patients were included in the study. Survival in patients with comorbidity was lower than in patients without comorbidity (p=0.0036). Survival of patients with a history of cerebrovascular occlusion was lower than those without (p=0.01). There was no statistically significant difference in survival between patients who received coagulation therapy in their history and patients (p>0.05). Survival analysis was performed according to the diagnosis of the patients in the emergency department. There was no statistical significance in terms of survival among patients with different diagnosis types (p=0.098). No statistically significant difference was found in the survival analysis for different application sites of thrombolytic therapy as emergency room, clinical service and intensive care unit (p=0.85). It was observed that doctors started thrombolytic practice as of 2017, and the number of applications increased over the years.

Conclusion: The favorable outcomes thrombolytic therapy have led an increase in the number of thrombolytic therapy conducted by ED clinicians while it was also seen that there was a reduction in morbidity and mortality over time.

Key words: Emergency department, thrombolytic treatment, comorbidity, mortality.

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5 Yıllık Trombolitik Tedavi Deneyimi

Öz

Amaç: Trombolitik tedavisi acil servis hastalarında hem hayat hem de hayati fonksiyonları kurtarıcı bir öneme sahiptir. Çalışmamızda amacımız 5 yıllık uzun bir periyotta 3. basamak bir hastanenin trombolitik uygulama tecrübesini ortaya koymaktır.

Yöntemler: 2017-2022 tarihleri arasında acil servise başvuran, trombolitik tedavisi verilen yetişkin hastalar seçildi. Hastaların demografik bilgileri, risk faktörleri, laboratuvar ve radyolojik parametreleri, tanıları ve trombolitik kullanımları incelendi.

Bulgular: 56 hasta çalışmaya dahil edildi. Komorbiditesi olan hastalarda sağkalım, komorbiditesi olmayan hastalara göre düşük bulundu (p=0.0036). Serebrovasküler oklüzyon öyküsü olan hastaların sağkalımı olmayanlara göre daha düşüktü (p=0.01). Öyküsünde önceden koagülasyon tedavisi alan hastalar ile almayan hastalar arasında sağkalım arasında istatistiksel anlamlı farklılık saptanmadı (p>0.05). Hastaların acil serviste aldıkları tanıya göre sağkalım analizi yapıldı. Farklı tanı tiplerine sahip hastalar arasında sağkalım açısından istatistiksel anlamlılık saptanmadı (p=0.098). Trombolitik tedavinin acil servis, klinik servis ve yoğun bakım olarak farklı uygulama yerleri için sağkalım analizinde istatistiksel olarak anlamlı farklılık saptanmadı (p=0,85). Doktorların trombolitik uygulamasına 2017 yılı itibariyle başladığı, yıllara göre uygulama sayısının arttığı görüldü.

Sonuç: Trombolitik tedavisi sonucu hastalarda bulunan olumlu sonuçlar acil tıp uzmanlarının trombolitik tedavisi uygulamasını yıllara göre artırmıştır, hastaların morbidite ve mortalitesinin de benzer şekilde azaldığı görülmüştür.

Anahtar kelimeler: Acil Servis, trombolitik tedavi, komorbidite, mortalite.

INTRODUCTION

Vascular emergencies are a frequently encountered group of disorders in emergency departments; in this group, ischemic stroke (CVO), acute myocardial infarction (AMI) and pulmonary thromboembolism are most important entities. The knowledge about thrombolytic therapy is helpful to emergency department (ED) clinicians in reducing morbidity and mortality in this group of disorders. In the thrombolytic therapy, the goal is the resolution of clots which can potentially lead life-threatening injuries. The major benefit is to ensure blood supply to tissues and improve short- and long-term survival by early restoration of blood flow[1]. In thrombolytic therapy, the agents used and the use in optimal duration after symptom onset are extremely important. For instance, intravenous thrombolytic therapy provides clinical benefit in acute ischemic stroke but the practice is not homogenous across countries[2].

Acute ischemic stroke accounts for 15% of all deaths in Turkey, comprising second leading cause of death[3]. The severity of stroke, coronary artery disease, atrial fibrillation, diabetes mellitus, advanced age and history of pneumonia are poor prognostic factors in acute ischemic stroke[4].

Alteplase was approved by US Food and Drug Administration in 1996. In Turkey, it was approved in 2006. The first national study on alteplase was published in 2016[5]. Regardless of mechanical thrombectomy, IV thrombolytic therapy is the first choice in patients fulfilling treatment criteria[6]. In many centers, thrombolytic use in acute myocardial infarction has been extremely decreased due to availability of angiography and door to balloon time up to 120 minutes. It is mostly performed in the referral centers[7,8]. It has been reported that only 50% of patients admitted with acute myocardial infarction are eligible to thrombolytic therapy[9]. Moreover, it was also

suggested that 10% of patients presented with pulmonary thromboembolism required thrombolytic therapy[10].

The ED clinicians have some concerns and differences in the experience about how intravenous (IV) tissue plasminogen activator (tPA) will be administered in above-mentioned settings. Thus, intravenous tissue plasminogen activator use hasn't been extensively used in the clinical practice among ED clinicians. In this study, it was aimed to assess the practice of thrombolytic therapy combined analysis of the patients' series from ED of a tertiary center and to detect mortality rate in patients treated with tPA by analyzing outcomes during follow-up.

Thrombolytic therapy is of important in saving life and vital functions in cerebrovascular diseases. Despite its well-known importance, the knowledge in what extent the well-known therapy and how it is reflected into practice will provide valuable benefits regarding therapeutic approach in the cerebrovascular diseases. In our study, it was aimed to share the experience of a tertiary center in thrombolytic therapy over 5 years.

METHODS

This retrospective, non-interventional, observational study included patients aged ≥18 years who presented to emergency department of Training and Research Hospital with acute ischemic stroke and underwent thrombolytic therapy between January 2017 and January 2022. In all patients, demographic data, risk factors, laboratory and radiology parameters, diagnoses and thrombolytic use were analyzed.

The inclusion criteria were age ≥18 years, presentation to emergency department of Training and Research Hospital, the diagnosis of acute ischemic stroke and undergoing thrombolytic therapy.

Overall, 58 patients were reviewed; 2 patients were excluded from analysis due to incomplete data; thus, final analysis included 56 patients.

Statistical Analysis

The data were analyzed using Jamovi Statistics Software version 1.6.18. Kaplan-Meier analysis was used to assess effects of diagnoses, settings of thrombolytic therapy, previous history of anticoagulant use, presence of comorbidity and different comorbid conditions on survival. The maximum follow-up was 90 days for survival analysis.

RESULTS

The demographic characteristics and laboratory data are summarized in Table 1 and Table 2, respectively.

Table I: Sociodemographic characteristics, length of ICU stay, comorbid conditions and complications of thrombolytic therapy

	N	Mean (±SD)	Median (25 - 75 P)
Age	56	63.071±15.6912	63 (50.500 to 77.000)
Length of ICU stay	56	4.339±11.1082	1 (1.000 to 3.500)

Variable\Statistic	Number of observations	Categories	Frequency per category	Rel. frequency per category (%)
Gender	56	Male	27	48.214
		Female	29	51.786
Comorbidity	56	Negative	37	66.071
		Positive	19	33.929
Hypertension	56	Negative	46	82.143
		Positive	10	17.857
Diabetes mellitus	56	Negative	49	87.500
		Positive	7	12.500
Coronary artery disease /Heart Failure	56	Negative	51	91.071
		Positive	5	8.929
Chronic renal failure	56	Negative	55	98.214
		Positive	1	1.786
Cerebrovascular occlusion	56	Negative	54	96.429
		Positive	2	3.571
Malignancy	56	Negative	55	98.214
		Positive	1	1.786
Chronic obstructive pulmonary disease	56	Negative	54	96.429
		Positive	2	3.571
Previous history of anticoagulant use	56	Negative	48	
		Positive	8	
Diagnosis	56	AMI	7	12.500
		PTE	30	53.571
		CVO	14	25.000
		AVTE	5	8.929
Thrombolytic complication	56	Negative	52	92.857
		Positive	4	7.143
Mortality		Negative	52	92.857
		Positive	4	7.143

ICU: Intensive Care Unit

Table II: Laboratory parameters

	N	Mean (±SD)	Median(25 - 75 P)
HGB	56	12.236±2.0935	12.5 (11.000 to 13.850)
WBC	56	11.371±4.7754	10.57 (7.795 to 14.075)
PLT	56	279.089±92.4903	270 (221.000 to 328.000)
PT	56	16.573±2.4055	16.15 (14.600 to 18.150)
APTT	56	29.007±5.5793	28.45 (26.150 to 30.950)
INR	56	1.211±0.1568	1.16 (1.085 to 1.305)

HGB: Hemoglabulin, WBC: White Blood Cell, PLT: Platelet, PT: Prothrombin Time, APTT: Actived Partial Thromboplastin Time, INR: International Normalized Ratio.

No significant difference was detected in survival according to gender (p=0.93). When comorbid conditions were reviewed, there was hypertension (17.8%), diabetes mellitus (DM) (12.5%), coronary artery disease (CAD) (8.9%), chronic renal failure (1.7%), cerebrovascular occlusion (3.5%), malignancy (1.7%) and chronic obstructive pulmonary disease (3.5%). Among these, no significant difference was

detected in survival between patients with or without history of hypertension (p=0.064). The survival was found to be significantly lower in patients with history of cerebrovascular occlusion (p<0.001).

When patients with or without comorbid condition were compared, it was found that the survival was significantly lower in patients with comorbid condition (90-days survival: 78.9% vs. 100%; p=0.036). No significant difference was detected in survival between patients with or without anticoagulant use (p>0.05). No significant difference was detected in survival rate between patients with or without history of previous anticoagulant use (p>0.05).

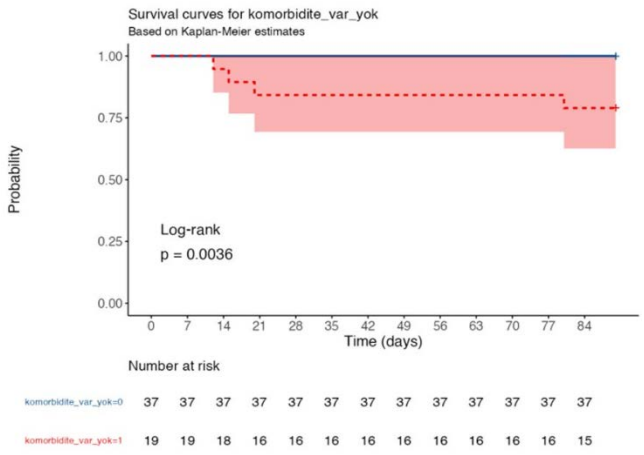

Figure 1: Kaplan-Meier survival analysis in patients with or without comorbid disease

A survival analysis was conducted according to ED diagnosis including acute myocardial infarction, pulmonary thromboembolism (PTE), cerebrovascular occlusion, peripheral arteriovenous thromboembolism. No significant difference was detected in the survival rate according to diagnosis (p=0.098). Again, no significant difference was detected in survival according to thrombolytic therapy settings (emergency department, ward or intensive care unit) (p=0.85).

It was seen that clinicians started to perform thrombolytic therapy by 2017 and number of thrombolytic therapies was increased over time (Table 3).

Table III: Number of thrombolytic therapies by clinicians over time

Year	Number of patients received thrombolytic therapy
2017	7
2018	10
2019	12
2020	19
2021	8
Total number of patients	**56**

DISCUSSION

In our study, 56 patients were given thrombolytic therapy using alteplase. In another study including 60 patients, thrombolytic therapy with alteplase was given to 20 CVO patients (33%) excluding those with clinical contraindication and good functional outcomes were reported in 40% of patients after month 3 (day 90). Authors suggested that the low rate might be due to small sample size[11]. In a study on 57 patients underwent thrombolytic therapy, it was reported that alteplase was the thrombolytic agent used in 75.4% of the patients and that 3-months mortality was 57.9% among all patients received thrombolytic therapy[12]. In our study, it was found that 90-days survival was 92% while mortality rate was 7.14% in 56 patients.

When survival analysis was considered in our study, it was found that the survival rate was significantly lower in the patients with history of cerebrovascular occlusion (p<0.001). however, no significant difference was detected in the survival across patients having different diagnoses including acute myocardial infarction (12.5%), PTE (53.5%), cerebrovascular occlusion 25.0%) or arteriovenous thromboembolism of extremities (8.9%). When patients with or without comorbid condition were compared, it was found that the survival was significantly lower in patients with comorbid condition (90-days survival: 78.9%

vs. 100%; p=0.036) (Figure 1). In our study, the comorbid diseases included hypertension (17.8%), DM (12.5%), CAD (8.9%), chronic renal failure (1.7%), cerebrovascular occlusion (3.5%), malignancy (1.7%) and chronic obstructive pulmonary disease (3.5%). In a study on 21 patients received thrombolytic therapy at ED settings, it was reported that there was hypertension in 57.1%, coronary artery disease in 33.3% and diabetes mellitus in 23.8%[2]. Unlike our study (mortality rate: 7.14%), the 90-days mortality was reported as 47.6% in the study[13], emphasizing importance of comorbidity.

Regarding comorbid conditions, no significant difference was detected in survival between patients with or without history of hypertension (p=0.064). On contrary, in a study on outcomes of IV thrombolytic therapy in CVO patients, Eryildiz ES et al. reported that the proportion of patients with history of DM and hypertension was higher in the group failed to achieve early neurological improvement[14]. In addition, found that early neurological improvement was strongly correlated with very good outcome or full recovery[14].

In CVO, it has been reported that poor outcome is independently associated with hypertension and DM[15]. Mechanistically, it is known that there is that DM increases free radical generation by leading anaerobic glycolysis, decreases fibrinolytic activity and increases permeability of blood-brain barrier and reperfusion injury, worsening outcome[16].

In a study on thrombolytic therapy, it was found that the complication rate was 7% and intracranial hemorrhage rate was 6%[12]. Similarly, we observed complications in 4 patients (7%) including intracerebral bleeding in 3 patients. In another study, major or minor bleeding complications related to the procedure developed in 18% of patients who received tPA therapy, and the mortality rate was 15%. and 6.3% of them were due to cerebral hemorrhage due to treatment complications[17].

It was found that thrombolytic therapy was delivered in ICU settings in 3 (75%) of 4 patients experiencing complication. In other words, mortality was higher in patients underwent thrombolytic therapy at ICU settings when compared to those underwent at ED settings. This suggests that early implementation of thrombolytic therapy at ED can be helpful to decrease mortality. In study supporting early implementation, it was reported that thrombolytic use between door and angiography in MI, at therapeutic time interval in CVO and within first 4 weeks in PTE decrease mortality[1].

In a study on thrombolytic interventions at ED, it was reported that there was no change in thrombolytic use by clinicians between 2016 and 2018 while it was seen that number of thrombolytic interventions was lower during first years, which, then, increased over time but not reached to desired levels (Table 3)[12]. It was found that, in urban populations, the most common reason for not delivering IV thrombolytic therapy is the time to implement thrombolytic therapy exceeds therapeutic time threshold[17]. Again, pre-hospital delay is among most common cause to implement IV thrombolytic therapy[17]. It is suggested that the poor awareness regarding stroke and IV thrombolytic therapy in the community plays major role in such delay[17].

It is important to raise awareness across citizens in addition to emergency medical staff, emergency department staff and clinicians. It is recommended to employ media tools including public service announcements about CVO, MI, PTE, thromboembolic diseases and thrombolytic therapies.

Limitation

Although this study has important contributions to available literature, it has some limitations

including small sample size, retrospective design, and lack of control group. Moreover, we have not reached any information about the exact root causes of mortality. Thus, the current findings did not yield strong inferences about the effects of comorbidities such as DM and CAD on mortality.

CONCLUSION

The favorable outcomes thrombolytic therapy have led an increase in the number of thrombolytic therapy conducted by ED clinicians while it was also seen that there was a reduction in morbidity and mortality over time.

Ethics Committee Approval: Permission was obtained from the Ankara City Hospital Ethics Committee with the date 13.04.2022 and number E2-22-1660.

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