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Analysis of Patients with Pulmonary Thromboembolism Who Received Thrombolytic Therapy in The Emergency Department

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Abstract

Introduction: Pulmonary embolism (PE) is a life-threatening but potentially reversible emergency condition that occurs as a result of the obstruction of pulmonary arteries. We aimed to assess the demographic features, laboratory data, and mortality rates of patients with pulmonary embolism who were administered thrombolytic therapy in this study.

Material and Methods: This was a retrospective study. It enrolled patients who received thrombolytic therapy for PE at the Emergency Medicine. The demographic data, comorbidities, physical examination findings and laboratory parameters of the patients with PE were retrospectively recorded.

Results: Sixteen patients were enrolled during the study. The most common symptoms were dyspnea (68.8%), syncope (62.5%), and chest pain (23.5%). Nine patients were brought to the emergency department with cardiac arrest, and 4 patients died at the emergency department. The 30-day mortality rate was 62.5%. When demographic and laboratory parameters were compared according to 30-day mortality among the patients who died and survived, there was no statistically significant difference in any parameter between the two groups. (p>0.05 for all parameters).

Conclusion: Systemic thrombolytic therapy is the first treatment option for patients with PE who are in shock or who have profound hypotension or hemodynamic instability. In this study, we showed that patients admitted to the emergency department with hemodynamic instability or cardiac arrest were abnormal in laboratory parameters, received lower doses of thrombolytic therapy and had higher mortality.

Key words: Pulmonary thromboembolism, thrombolytic therapy, emergency

Introduction

Pulmonary embolism (PE) is a life-threatening but potentially reversible emergency condition that occurs as a result of the obstruction of pulmonary arteries[1]. PE is a common cardiopulmonary disease with an annual incidence of more than 0.1% in the United States of America[1]. The mortality rate of acute PE is between 7% and 11%[2]. It is more common among males in all age groups, and its mortality is higher in male sex and among the elderly[2,3].

The mortality and morbidity rates of PE have been reduced over the past years, particularly by advances in diagnosis, risk assessment, and treatment as well as anticoagulation. Pulmonary embolism has no specific clinical and physical examination findings, but high suspicion is essential for diagnosis. Ventilation/perfusion (V/Q) scintigraphy, computerized tomography angiography (CTA), lower extremity venous Doppler ultrasonography (USG), and echocardiography (ECHO) are the diagnostic tools with increased reliability and effectiveness[2, 3]. Since it is a disease with high mortality and morbidity, anticoagulant therapy is mostly initiated when embolism is suspected. Unless there is an absolute contraindication to thrombolytic therapy, it is the most effective treatment option for moderate-to-high risk PE[3, 4]. However, adverse events with thrombolytic therapy which may result in death are reported in 15-20% of cases[5].

Patients with high-risk PE presenting with shock or hypotension are at high risk of death at the hospital, particularly within a few hours after admission[6]. Therefore, thrombolytics should be given to all patients with high-risk PE unless there is an absolute contraindication[3, 4]. In this study, we aimed to assess the demographic features, laboratory data, and mortality rates of patients with pulmonary embolism who were administered thrombolytic therapy.

Materials and Method

This was a retrospective study. Ethical approval for this study was obtained from local Hospital Ethics Committee (2012-KAEK-15/2111, 10/06/2020). It enrolled patients who received thrombolytic therapy for PE at the Emergency Medicine Clinic between 01.01.2014 and 01.11.2019. At our clinic, thrombolytic therapy is administered to hemodynamically unstable patients in compliance with the current

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guidelines. Alteplase (Actilyse®) 100 mg is infused for 2 hours or, in patients with cardiac arrest, it is administered as intravenous (IV) bolus at a dose of 50 mg.

The demographic data, comorbidities, previous surgeries, vital signs, physical examination findings, laboratory parameters, and consultations of the patients with PE were retrospectively recorded from the hospital automation system and the medical records. Deaths at the emergency department and by the 30th day were also recorded. The patients with missing medical data and those who were not administered thrombolytic therapy were excluded from the study.

Statistical Analysis

Study data were analyzed using IBM SPSS 20.0 (Chicago, IL, USA) statistical software. Normality of discrete and continuous variables was tested using Kolmogrov Smirnov test. Descriptive statistics included median and IQR25-75 (interquartile range) for discrete and continuous variables and number and (%) for categorical variables. Categorical variables were compared using Chi-square test and continuous variables using Mann Whitney-U test.

The results were considered statistically significant at a level of $p<0.05$.

Results

Sixteen patients were enrolled during the study period. Seven (43.8%) patients were women, and the median age of the patients was 65 years (IQR 25-75%: 46.2-84.7 years). The most common comorbidity was hypertension (31.3%). The most common symptoms were dyspnea (68.8%), syncope (62.5%), and chest pain (23.5%). Seventy-five percent of the patients had hypotension that required inotrope infusion. Nine patients were brought to the emergency department with cardiac arrest, and 4 patients died at the emergency department. The 30-day mortality of our 16 patients was 62.5% (n=10). Eight of these patients (80%) were brought to the emergency department with cardiac arrest. The 30-day mortality rate of our patients who were admitted as cardiac arrest was 88.8% (n=8).

The demographic features and some laboratory results of the patients were shown in Table-1.

The laboratory results of the patients were shown in Table 2.

A comparison of age, sex, thrombolytic doses, and laboratory parameters between the deceased and surviving patients at the end of the 30th day revealed that although deceased patients had lower hemoglobin, pH, pCO2, and HCO3, and a higher white blood cell (WBC), pCO2, lac-

Table 1: Demographic data of patients

Variables	N=16
Age, years median (IQR25-75)	65 (46.2-84.7)
Gender n (%)	
Female	7 (43.8%)
Male	9 (56.3%.)
Co-morbidities n (%)	
Hypertension	5 (31.3%)
Diabetes mellitus	4 (25%)
Chronic obstructive pulmonary disease	1 (6.3%)
Coronary artery disease	3 (18.8%)
Heart failure	2 (12.5%)
Chronic renal disease	3 (18.8%)
Risk factors for thromboembolism n (%)	
Lower extremity fracture	4 (25%)
Previous surgery	1 (6,3%)
Deep vein thrombosis	3 (18.8%)
Malignancy	1 (6,3%)
Symptoms n (%)	
Dyspnea	11 (68.8%)
Syncope	10 (62.5%)
Chest pain	4 (23.5%)
Cardiac arrest	9 (56.3%)
Vital sings median (IQR25-75)	
Systolic blood pressure mmHg	80 (53.2-98.5)
Diastolic blood pressure mmHg	50 (33.7-61.2)
Heart rate /minute	105 (66-121)
Glasgow Coma Scale, median (IQR25-75)	5.5 (3-15)
Elevation of troponin n (%)	9 (56.3%)
Inotrope requirement n (%)	12 (75%)
Outcome n (%)	
Mortality in emergency department	4 (25%)
ICU hospitalization	12 (75%)
Thrombolytic Dose n (%)	
50mg	9 (56.3%)
100 mg	7(43.7%)
Thrombolytic Dose mg median (IQR 25-75)	50 (50-100)
Stay of hospital length, day median (IQR 25-75)	4 (0-7)
30-day mortality n (%)	10 (62.5%)

Table 2: Laboratory findings of all patients

Variables, median (IQR25-75)	
Hemoglobin	13.2 (12.8-14.4)
White blood cell	12.6 (8.8-13.9)
Platelet	205 (126-282)
Ph	7.24 (7.13-7.33)
PO2	47(28.5-67)
PCO2	39.3 (31.5-56.4)
HCO3	19 (13.5-20.6)
Lactate	5.7 (4.1-8.1)
Glucose	149 (130-242)
Aspartate Transaminase	48 (11-84.5)
Alanine Amino Transferase	39.5 (21.7-84)
Creatinin	1.08 (0.93-1.34)
Lactate dehydrogenase	389 (315.5-453.7)
Albumin	3.75 (3-3.9)

tate, glucose, Alanine Amino Transferase (ALT), Aspartate Transaminase (AST), creatinine, and troponin level, statistical significance was not reached for any parameter ($p>0.05$ for all parameters). The patients who died were administered a lower thrombolytic dose (Table 3).

Discussion

Pulmonary embolism represents a disease spectrum from an asymptomatic condition to death. Signs and symptoms of PE depend on a patient's cardio-pulmonary reserve and age as well as the location, size, unilateral or bilateral pulmonary vascular involvement, and the recurrence of a thrombus[7, 8]. Dyspnea is the most common symptom[9]. It was also the most common symptom in our patient group. The most remarkable aspect of our study is the high number of patients who had a cardiac arrest. During the study period, 252 patients were diagnosed with PE, 6.3% of whom received thrombolytic therapy. About half of our patients were brought to the emergency department in cardiac arrest status. As our hospital does not contain a chest disease clinic, patients diagnosed with PE are referred to another center for admission to a regular ward or intensive care unit before or after thrombolytic therapy, with the latter to be administered at the referral center whenever possible. We rapidly administer thrombolytic therapy particularly to patients with pre-arrest status or embolism-induced arrest, which, to our opinion, led to a high number of cases admitted with cardiac arrest.

Thrombolytic medications are the pharmacological substances that convert plasminogen to plasmin and actively lyse a thrombus. Early thrombus resolution rapidly fixes increased pulmonary arterial pressure/resistance and accompanying right ventricular dysfunction. Thrombolysis is achieved more rapidly by thrombolytic therapy than heparin, particularly in the first 24 hours [10, 11]. Patients with hemodynamic instability constitute 5-10% of all cases of pulmonary embolism[12, 13]. Seventy-five percent of our cases had hypotension requiring inotrope therapy. Right ventricular dysfunction is found in 30-50% of cases. The presence of both parameters indicates a poor prognosis[13-15]. Thrombolytic therapy reduces mortality by normalizing hemodynamic parameters and right ventricular function. However, its effect on long-term mortality and prognosis is controversial[16]. Besides, an increased risk of major bleeding associated with the use of thrombolytics should also be considered. Thrombolytic agents used for PE are the ones that have been most extensively studied for Acute PE and include recombinant tissue plasminogen activator (tPA), streptokinase, and recombinant human urokinase. Alteplase is used in our clinic. Intravenous alteplase 100 mg is administered via continuous infusion for 2 hours. In more urgent cases (for example, precardiac arrest), it is recommended to administer tPA as a bolus at first and 15th minutes or as a 20 mg IV bolus followed by infusion of 80 mg tPA for 2 hours[6, 17, 18]. However, none of these regimens has been compared with the classical two-hour tPA infusion. Evidence from small randomized studies, on the other hand, suggests that shorter infusions

Table 3: Comparison of laboratory and thrombolytic doses according to patients' 30-day mortality

Variables, median (IQR25-75)	Survived (n=6)	Non survived (n=10)	p value
Age, year	58 (37-87)	65 (50.7-82.5)	0.586
Gender n (%) Male	 4 (57.1%)	 5 (50%)	 0.581
Hemoglobin	13.8 (13.2-16.4)	12.9(10.9-14.2)	0.111
White blood cell	9.3 (7.4-13.1)	13.2 (10.3-15.4)	0.205
Platelet	183 (123-267.5)	219 (153-285.5)	0.640
Ph PO2 PCO2 HCO3	7.28 (6.95-7.36) 49 (32.7-69) 47.1 (35.1-79.7) 19.8 (12.4-20.2)	7.20 (7.13-7.30) 44.7 (24-71) 37.8 (25-52.9) 17.5 (13.5-21.4)	0.589 0.877 0.280 0.998
Lactate	3.8 (2.1-5.9)	6.5 (4.8-9.6)	0.064
Glucose	131 (122-188.5)	172 (137-345)	0.125
Aspartate Transaminase	39 (11.5-98.5)	61 (13.5-92)	0.739
Alanine Amino Transferase	34 (20.5-53)	42 (25.5-148)	0.317
Creatinin	1.06 (1-1.2)	1.28 (0.86-1.79)	0.894
Lactate dehydrogenase	451 (345-572)	349 (252-397.5)	0.149
Albumin	3.6 (3.1-3.9)	3.7 (2.9-3.95)	0.941
Elevation of troponin n (%)	2 (33.3%)	7 (70%)	0.302
Thrombolytic Dose	75 (50-100)	50 (50-100)	0.705

(i.e. ≤2 hours) more rapidly achieve thrombolysis and are associated with lower bleeding rates compared to longer infusions [6,17]. Kiser et al. reported that half-dose Alteplase, as compared with the full dose, was associated with similar mortality and major bleeding rates although patients who received a half dose more commonly required dose adjustment. According to these results, the authors stressed that questions remained whether half dose Alteplase has similar efficacy as the full dose[19]. It is recommended that thrombolytic therapy be used as bolus infusion in patients presenting with PE-related cardiac arrest[6].

We observed that the majority of our deceased patients were brought to the emergency department with cardiac arrest or were more hemodynamically unstable or had more abnormal laboratory parameters compared to surviving patients. We similarly found that 80% (n=8) of the deceased patients (30-day mortality) presented to the emergency department with cardiac arrest, and thus this patient group received a lower thrombolytic dose than the surviving patients.

It has been shown that moderate-to-severe hypoxemia caused by acute PE leads to hepatopathy, liver function abnormalities, and reduced albumin synthesis[20,21]. It has also been found that these abnormalities were more profound in patients with severe hypoxemia and hemodynamic instability than those with mild hypoxemia. In a study reported by Aslan where liver function tests (LFTs) were investigated among patients with pulmonary embolism, it was found that similar to our results, LFT abnormalities were more common in patients with severe hypoxemia and hemodynamic compromise[20]. Identification of apparently stable patients at high risk of rapid clinical deterioration is critically important for optimizing decisions concerning the intensive care admission from the emergency department, and treatment. For this purpose, various potential prognostic markers like troponin, brain natriuretic peptide (BNP), and echocardiogram have been studied, and troponin and lactate elevations were found to correlate to mortality[22-24]. Lactate is known to predict clinical outcomes in patients with sepsis and trauma. Considering that pulmonary embolism (PE) may lead to lactic acidosis via hypoperfusion or hypoxia, several studies have tested lactate levels for mortality prediction in PE[22,23]. In a prospective study reported from Italy assessing lactate levels for mortality prediction, a lactate level above 2 mmol/L without concomitant shock or hypotension had a positive predictive value of 16% and a negative predictive value of 98% for the prediction of 30-day all-cause mortality[22]. Likewise, a higher lactate level was shown to correlate to shock development, the need for mechanical ventilation, and vasopressor administration[23]. Also, our deceased patients had a saliently higher [6.5 mmol/L (IQR 25-75, 4.8-9.6)] lactate level than the survivors. Our results revealed that most of the deceased patients presented to the emergency department with cardiac arrest were hemodynamically more unstable and had more abnormal laboratory parameters.

Limitations

Our study has some limitations. First of all, it was a single-center study, with its results being non-generalizable to all centers. Secondly, it was a retrospective study, thus deficient or erroneous data obtained from hospital records may have affected our study results. Also because of the patient diagnoses (ICD codes) were not entered properly, a smaller number of patients may have been included in the study.

Although there was some difference between the laboratory parameters of the deceased and surviving patients, they did not reach statistical significance, which may have stemmed from the small numbers of patients in the study groups, thereby widening the confidence intervals.

Conclusion

Systemic thrombolytic therapy is the first treatment option for patients with PE who are in shock or who have profound hypotension or hemodynamic instability. Herein, we showed that, among patients presenting to the emergency department with greater hemodynamic instability or cardiac arrest, laboratory parameters were abnormal, which led to the administration of a lower dose of thrombolytic therapy and higher mortality.

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