EFFICACY OF TISSUE PLASMINOGEN ACTIVATOR, HEPARIN AND STREPTOKINASE IN PATIENTS WITH SUB MASSIVE PULMONARY EMBOLISM IN A TERTIARY CARE CARDIAC HOSPITAL

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ABSTRACT

Objective: To determine the clinical characteristics and outcomes of 25 cases of pulmonary embolism in relation to use of thrombolytic and anticoagulants.

Study Design: Case series study.

Place and Duration of Study: Adult cardiology department of Armed Forces Institute of Cardiology & National Institute of Heart Diseases from Oct 2017 to Jan 2018.

Material and Methods: Total 25 patients with pulmonary embolism were included in the study using consecutive sampling technique. Clinical characteristics and outcomes of the patients were noted and analyzed. SPSS-23 was used for data analysis.

Results: Twenty five cases of acute pulmonary embolism were included in our study and were admitted to the coronary care unit of hospital during the study period. Mean age of patients was 42 ± 18.32 years with minimum age 20 years and maximum 83 years. There were 19 (76.0%) male patients while 6 (24.0%) female patients. Most common NYHA class with which patients presented was, class-II 10 (40%) followed by class-III 8 (32%). The most common CT pulmonary angiogram finding of the patients was bilateral segmental embolism 17 (68.0%). Out of 25 patients, 12 (48.0%) patients received streptokinase and four (16%) received tissue plasminogen activator. Four patients were found to have deep venous thrombosis. Mortality was 20%.

Conclusion: Acute pulmonary embolism is a relatively common medical emergency and accurate diagnosis in early period can help institute appropriate thrombolytic therapy to maximally benefit the patients.

Keywords:, CT pulmonary angiogram, Deep venous thrombosis, NYHA class, Pulmonary embolism

INTRODUCTION

Pulmonary embolism (PE) is a relatively common cardiovascular emergency occurring in 60 to 112 of every 100,000 individuals[1]. About 430,000 people each year in Europe are affected by pulmonary emboli. In the United States between 300,000 and 600,000 cases occur each year, which results in between 50,000 and 200,000 deaths[2]. Rates are similar in males and females. They become more common as people get older. It is the third most common cause of cardiovascular mortality and is responsible for 100,000 to 180,000 deaths annually[1]. The prevalence of pulmonary embolism among hospitalized patients in the United States, according to data collected between 1979 and 1999, was 0.4% though only 40–53 per 100 000 persons were diagnosed with pulmonary embolism per year[3]. By occluding the pulmonary arterial bed it may lead to acute life-threatening but potentially reversible right ventricular failure[4]. Pulmonary embolism is a difficult diagnosis that may be missed because of non-specific clinical presentation. However, early diagnosis is fundamental, since immediate treatment is highly effective. PE should be part of differential diagnosis in patients who present with new or worsening dyspnoea, chest pain or hypotension. Based on physician's level of suspicion, the diagnostic workup may include a clinical decision rule, biomarkers (e.g., d-dimers) and/or imaging modalities such as computed tomographic pulmonary angiography (CTPA) or

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a ventilation perfusion scan. Additional evaluations may be performed with Troponins, B-type natriuretic peptide (BNP) and/or echocardiography. PE is commonly classified as massive (high-risk), submassive (intermediate-risk) and low risk to help determine the required treatment. Massive PE is defined as suspected or confirmed PE in the presence of shock, sustained hypotension, pulselessness or persistent profound bradycardia. Sub- massive PE is defined as suspected or confirmed PE with right ventricular dysfunction in the absence of shock[5]. Epidemiology, predisposing factors, natural history, and the pathophysiology of pulmonary embolism have been described more extensively worldwide[4,6,8]. Depending on the clinical presentation, initial therapy is primarily aimed either at life- saving restoration of flow through occluded pulmonary arteries (PA) or at the prevention of potentially fatal early recurrences. Both initial treatment and the long-term anticoagulation that is required for secondary prevention must be justified in each patient by the results of an appropriately validated diagnostic strategy[6,7,9]. Pulmonary embolism and deep venous thrombosis are two clinical presentations of venous thrombo-embolism (VTE) and share the same predisposing factors. In most cases pulmonary embolism is a consequence of DVT. Among patients with proximal DVT, about 50% have an associated, usually clinically asymptomatic pulmonary embolism at lung scan[5,7,8]. In about 70% of patients with Pulmonary embolism, DVT can be found in the lower limbs if sensitive diagnostic methods are used[10]. The risk of death related to the initial acute episode or to recurrent PE is greater in patients who present with pulmonary embolism than in those who present with DVT. According to prospective cohort studies, the acute case fatality rate for Pulmonary embolism ranges from 7 to 11%[11]. Although Pulmonary embolism can occur in patients without any identifiable predisposing factors, one or more of these factors are usually identified (secondary pulmonary embolism)[12-14]. The proportion of patients with idiopathic or unprovoked pulmonary embolism was about 20% in the International cooperative pulmonary embolism registry (ICOPER)[15]. Patient-related predisposing factors include age, history of previous VTE, active cancer, neurological disease with extremity paresis, medical disorders causing prolonged bed rest, such as heart or acute respiratory failure, and congenital or acquired thrombophilia, hormone replacement therapy and oral contraceptive therapy[16-18]. An association between idiopathic pulmonary embolism and cardiovascular events, including myocardial infarction and stroke, has recently been reported[12,17]. Reports of a high risk of pulmonary embolism among obese people, smokers and patients affected by systemic hypertension or metabolic syndrome have renewed interest in the link between arterial thrombo-embolism and VTE[9,10].

MATERIAL AND METHODS

A Case series study was carried out at Armed forces Institute of Cardiology (AFIC/ NIHD) Rawalpindi from Oct 2017 to Jan 2017. A total of 25 patients of pulmonary embolism were included in the study, using consecutive sampling technique. Data collection tool was used to collect the different variables. Data was entered analyzed using SPSS Version 23.

RESULTS

Twenty five cases of acute pulmonary embolism were included in the study who were admitted in the coronary care unit (CCU) during study period. Mean age of patients was 42 ± 18.3 years with minimum age 20 years and maximum 83 years. There were 19 (76.0%) male patients while 6 (24.0%) female patients. Most common NYHA class with which patients presented was, class-II 10 (40%) followed by class-III 8 (32%). The most common CT pulmonary angiogram finding of the patients was bilateral segmental embolism in 17 (68.0%) as shown in table-I. Out of 25 patients, 12 (48.0%) patients received streptokinase. Four patients were found to have deep venous thrombosis. Mortality was 20.0%

(n=5). Chi-square test was applied to find out the association between mortality and different variables. Results showed that only NYHA class findings was statistically significant (*p*-value<0.05) with mortality as shown in table-II.

Table-I: Frequencies (%) of characteristics of patients with pulmonary embolism.

Variables	Frequency (%) (n=25)
Age (Mean ± SD)	44 (± 18.52)
Outcome	
Dead	5 (23%)
Alive	20 (76%)
Gender	
Male	19 (76%)
Female	6 (24%)
NYHA	
I	2 (10%)
II	10 (50%)
III	4 (20%)
IV	4 (20%)
dDimers	
<200	2 (8%)
>200<400	13 (52%)
>400<800	9 (36%)
>1200	1 (4%)
Treatment	
SK	12 (48%)
Heparin	9 (36%)
tPA	4 (16%)
Echo	
Dilated RA/RV	20 (80%)
Normal	5 (20%)
DVT	
Yes	4 (16%)
No	21 (84%)
CTPA	
Bil segmental embolism	16 (64%)
Saddle Embolus	1 (4%)
Bil massive	2 (8%)
Lobar embolism	6 (24%)

DISCUSSION

Massive PE was previously defined by anatomical criteria: >50% obstruction of pulmonary vasculature or occlusion of 2 or more lobar arteries. It is now more commonly defined by hemodynamic instability, which is a function of both PE size and underlying cardiopulmonary status. Massive acute pulmonary embolism is now defined as sustained hypotension (systolic blood pressure <90 mmHg for at least 15 min or requiring inotropic support not due to a cause other than PE such as arrhythmia, hypovolemia, sepsis or LV dysfunction, pulselessness, or persistent profound bradycardia (heart rate <40 bpm with sign and symptoms of shock)[10]. Acute

pulmonary embolism leads to an abrupt rise in pulmonary vascular resistance. Right ventricular contractile function is compromised and right ventricular failure ensues. This vicious cycle of cardiogenic shock is augmented by concomitant hypoxia, which inevitably leads to cardiovascular collapse. The interval from the onset of symptoms to death is relatively short. In patients with massive pulmonary embolism, 50% died with in 30 minutes, 70% died within 1hour, and more than 85% died within 6 hours of the onset of symptoms. Therefore, the window for obtaining a definitive diagnosis is small. In an optimal setting, the diagnosis of pulmonary embolism can be made on the basis of the history and physical examination along with selective tests, such as electrocardiography (ECG) to rule out myocardial infarction, chest radiography to rule out pneumothorax, and an arterial blood gas analysis to strengthen the diagnosis[17]. When the diagnosis of massive pulmonary embolism is made, medical or surgical treatment must be initiated immediately. If the patient is in remote area, the decision to perform embolectomy may be made primarily on clinical impression. Thrombolysis is also an established therapy for massive pulmonary embolism[17,18,28]. Definitions of sub-massive PE vary in literature and intermediate risk PE is sometimes used in preference to 'sub-massive'. It is defined as acute PE without systemic hypotension (SBP >90 mmHg but with RV dysfunction or myocardial necrosis)[28]. In PEITHO trial intermediate risk PE was defined as presence of RV dysfunction or a positive Troponin[17]. In MOPPET trial moderate PE was defined as the presence of signs and symptoms of

Table-II: Association between outcome and independent variables.

Variables	Outcome		X^2 Results
	Alive(n=20)(%)	Dead (n=5)(%)	
Gender			
Male	15 (75%)	4 (80%)	p=0.811
Femal	5 (25%)	1 (20%)	
dDimer			
<200	1 (5%)	1 (20%)	
>200 - <400	10 (50%)	4 (80%)	p=0.184
>400 - <800	8 (40%)	0	
1200	1 (5%)	0	
NYHA			
I	2 (10%)	0	
II	10 (50%)	0	p=0.05
III	4 (20%)	4 (80%)	
IV	4 (20%)	1 (20%)	
DVT			
Yes	4 (16%)	1 (20%)	p=0.57
No	16 (84%)	4 (80%)	
Echo			
Dilated RA/RV	15 (75%)	5 (100%)	p=0.75
Normal	5 (25%)	0	
Treatment			
SK	8 (40%)	4 (80%)	
Heparin	9 (45%)	0	p=0.162
tPA	3 (15%)	1 (20%)	

PE plus computed tomographic pulmonary angiographic involvement of >70% involvement of thrombus in >2 lobar or left or right main pulmonary arteries or by a high probability ventilation/perfusion scan showing ventilation/ perfusion mismatch in >2 lobes[12,18]. Sub-massive PE accounts for 20% of all PEs with in-hospital mortality of 2-5%. There is evidence from registries data that the short term mortality rate directly attributable to sub-massive PE treated with heparin anticoagulation is probably <3%. It accounts for most deaths from PE, leads to long term morbidity especially chronic pulmonary hypertension and worst functional outcome. Cho JH et al, found that haemodynamically stable patients with PE, 37% have RV dysfunction on echo and also found higher short term mortality in this group (Odds ratio 2.29; 13.7 vs 6.5 without RV dysfunction)[15]. RV dysfunction and elevated troponins are also predictors of poor outcome in sub-massive PE[18]. As such a smaller PE in a patient with poor cardiopulmonary reserve could produce similar outcomes to a larger PE in a patient without prior cardiopulmonary disease[17].

The use of thrombolytic agents for the treatment of sub-massive PE is somewhat debateable the limited documented benefit (e.g. improved hemodynamics, potential for less chronic pulmonary hypertension) must be weighed against the increased risk of life-threatening hemorrhage and the availability of other therapies (e.g. catheter-directed thrombolysis or clot retrieval)[25]. The present study was conducted to document efficacy of thrombolytic and anticoagulant agents in sub-massive PE. We used Streptokinase and tissue plasminogen activator and heparin and studied their use in terms of efficacy, resolution of symptoms, improvement in haemodynamic profile and echocardiographic parameters. This is an ongoing study and presently data of initial twenty five patients is being analyzed and presented. Streptokinase was used in 12 patients in a dose of 250,000 initial bolus followed by 100,000 units/hour for next 24 hour. Out of these twelve patients, 8 survived and four succumbed to their illness. Tissue plasminogen activator (tPA) was used in four patients in a dose of 100 mg over 2 hours preceded by 10 mg bolus. Out of these four patients, three made an uneventful recovery and one patient died. In the remaining nine patients only heparin was use in a dose of 18 units /Kg/hour preceded by intravenous bolus of 5000 units. Tissue plasminogen activator was used preferentially in young soldiers who developed venous thromboembolism (VTE) at high altitude and later confirmed on CT pulmonary angiogram. The patient who died after tPA administration was because of massive haemoptysis which is in line with higher bleeding risk after thrombolysis[1,15,27]. Patients who were given heparin only did reasonably well as no patient died in this group. This was well demonstrated in earlier studies like MAPPET-3 trial which compared heparin with alteplase in sub-massive pulmonary embolism and showed no difference for in-hospital mortality (3.4% versus 2.2%; p=0.71)[27]. However, in PEITHO trial which compared Heparin with Tenecteplase, substantial reduction in combined end point of early mortality or haemodynamic collapse was seen but at the cost of significant increase in major haemorrhage (including intracranial haemorrhage)[17].

CONCLUSION

Cardiologists may be asked to manage patients with massive and sub-massive PE because cardiovascular medical specialists are trained to treat hemodynamic derangements with a variety of interventional and pharma- cological approaches. A rapid and accurate assessment of risk and a decisive treatment plan should be established. Fortunately, fibrinolysis, catheter intervention, and possible col-laboration with cardiac surgeons for desperately sick patients are tools that will assist cardiovascular specialists in maximizing the likelihood of prompt and complete recovery in these seriously ill patients.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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