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Long-term follow-up results of unfractionated heparin infusion treatment for submassive pulmonary thromboembolism

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SUMMARY

OBJECTIVE: Treatment options for submassive pulmonary thromboembolism cases vary depending on the patient's hemodynamic stability, comorbidities, and bleeding risk. The long-term effect of unfractionated heparin treatment on pulmonary hypertension and mortality is unclear. The aim of this study was to investigate the long-term effect of unfractionated heparin treatment on pulmonary thromboembolism.

METHODS: This is a cross-sectional study with 22 patients who were diagnosed with submassive pulmonary thromboembolism and followed up at the outpatient clinic between 2016 and 2020 and received unfractionated heparin treatment.

RESULTS: Mean pulmonary artery pressure was 53±13.6 mmHg during hospital admission and 42.7±13.4 mmHg at hospital discharge. There was a statistically significant decrease in D-dimer and pulmonary artery pressure levels before and after treatment (p=0.001). At the end of one year, pulmonary artery pressure was considered high in three patients of this study.

CONCLUSION: Our study suggests that unfractionated heparin is safe in the treatment of submassive pulmonary thromboembolism in terms of bleeding risk and reduces pulmonary artery pressure.

KEYWORDS: Pulmonary embolism. Unfractionated heparin. Long-term effect. Pulmonary hypertension.

INTRODUCTION

Pulmonary thromboembolism (PTE) presents with different clinical characteristics, ranging from asymptomatic cases to those who die within hours due to hemodynamic instability. Due to these clinical differences, treatment approaches also vary. "Risk assessment" is the most critical step in determining the appropriate treatment approach for acute PTE cases. "Risk," as defined herein, is the risk of death associated with the acute PTE. Therefore, distinguishing the patient diagnosed with acute PTE as high risk (massive), intermediate risk (submassive), or low risk (nonmassive) in terms of early mortality can help determine the treatment options and prognosis[1]. Low-molecular-weight heparin (LMWH) and oral anticoagulants are often preferred for the treatment of nonmassive PTE and thrombolytics for massive PTE[2]. Treatment options for submassive PTE cases vary depending on the patient's hemodynamic stability, comorbidities, and bleeding risk[3]. Systemic anticoagulation, LMWH, oral anticoagulants, catheter-directed thrombolysis, half-dose thrombolysis (50 mg tPA), and inferior vena cava (IVC) filters are the treatment options for submassive PTE[4,5]. Unfractionated heparin (UFH) treatment was commonly used in the past for submassive PTE but is less preferred nowadays due to newer treatment options that are easier to follow. Studies investigating the effect of UFH infusion therapy on pulmonary hypertension (PHT) in the long term are insufficient.

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In this article, we examined the demographic characteristics, symptoms, comorbidities, and risk factors of patients with submassive PTE treated with UFH infusion; the effect of heparin on platelet count and blood count in the early (3–5 days) and late (15 days) periods; and the developmental status of chronic thromboembolic PHT at the end of one year.

METHODS

In our study, data from 22 patients who received UFH infusion therapy after admission to the intensive care unit (ICU) with a diagnosis of submassive PTE and were subsequently followed up in the outpatient clinic for one year were retrospectively analyzed between 2016 and 2020 according to the 2015 Turkish Thoracic Society PTE diagnosis and treatment consensus report.

Study population

The diagnosis of PTE was made in the emergency department using contrast-enhanced dynamic chest computed tomography (image). Patients with findings consistent with submassive PTE on echocardiography (ECHO) were included in this study. In addition, patients with findings of right ventricular dilatation, paradoxical motion and deviation of the septal wall to the left, moderate or severe hypokinesis suggestive of right ventricular dysfunction, mobile thrombus in the right atrium, PHT, and patent foramen ovale at ECHO, despite normal systemic blood pressure, were considered submassive PTE. Patients' symptoms on admission, concomitant diseases and risk factors, hemoglobin and platelet counts, troponin and D-dimer levels, arterial blood gas values, and ECHO findings on admission to the ICU and on discharge from the hospital were obtained from hospital records. Additionally, follow-up results of ECHO at months one, three, and six and at the end of the first year, as well as D-dimer levels at the end of treatment, were obtained from outpatient records. Subsequently, all collected data were statistically analyzed.

Treatment protocol

All patients were followed up in the ICU after ECHO was performed in the emergency department. After observing the basal activated partial thromboplastin time (aPTT) values of the patients, a bolus of 80 IU/kg intravenous (i.v.) followed by a heparin infusion of 18 IU/kg/h was started. In the first 24 h, treatment was supplemented with warfarin when the aPTT value reached 45–70. The aPTT level was measured every 6 h for the first 24 h and daily after reaching the desired level. If internalized normal ratio (INR) values of 2–3 were detected within the 24-h interval, heparin was discontinued and treatment with warfarin was continued. Thus, all patients received warfarin therapy for at least six months.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 15.0. A homogeneity test was performed on numeric variables. Independent sample *t*-tests were used for numerical parameters. Paired sample *t*-test was used to test whether there was a difference in the mean of numerical variables at the beginning (baseline) and end of treatment. Pearson's correlation analysis was performed for distributed homogeneous variables. Nonhomogeneous variables were analyzed using nonparametric tests. A $p<0.05$ was considered significant.

RESULTS

Of the 22 patients followed up and treated with a diagnosis of submassive PTE, 11 were females and 11 were males. The mean age of the cases was 53.5±20 years. The most common symptoms on admission were shortness of breath (n=22), central chest and flank pain (n=18), palpitations (n=16), and cough (n=15), while the most common risk factors were immobilization (n=12), deep vein thrombosis (n=10), and orthopedic surgery (n=6) (Table 1).

Blood gas values of patients on admission were as follows: pH: 7.46±0.05, PO_2: 66.1±14.1 mmHg, PCO_2: 32.4±5.2 mmHg, HCO_3: 22.1±3.1 mEq/L, saturation O_2: 92±4.7%. Hypoxemia (PO_2<80 mmHg) was observed in 18 patients, and hypocapnia (PCO_2<35 mmHg) was observed in 15 patients.. D-Dimer levels were 3.67±2 ng/mL before treatment and 0.49±0.59 ng/mL at the end of treatment. D-Dimer levels remained high (>0.5 ng/mL) in two patients at the end of treatment. Of the patients whose D-dimer levels remained high, one had prior cerebrovascular disease and coronavirus 2019 disease, and one had breast carcinoma.

The mean troponin level on admission was 42.3±50.3 ng/mL. Troponin levels were above normal laboratory values in 12 patients (troponin 0–14 ng/mL).

Mean hemoglobin on hospital admission was 12.2±2.1 and 11.2±1.9 g/dL on day three, 11.7±1.8 g/dL on day five, and 11.9±1.6 g/dL on day 15. The mean platelet count was 291,500±95,700/mL on admission, 295,000±159,100/mL on day 3, 307,300±158,000/mL on day 5, and 341,800±159,000/mL on day 15. No patient experienced a decrease in hemoglobin level or platelet count during the early (on days 3–5) and late (on day 15) phases with heparin.

Mean pulmonary artery pressure (PAP) was 53±13.6 mmHg on ECHO in the emergency department during hospital admission. PAP was found to be 42.7±13.4 mmHg at hospital discharge (ECHO) (Table 2). There was a statistically significant decrease in D-dimer and PAP levels before and after treatment. Notably, 19 patients with D-dimer levels below 0.5 ng/mL had PAP levels of 20 mmHg and below at the end of treatment. At the end of 1 year, PAP was considered high in three patients. It was determined that three patients underwent V/P scintigraphy and were evaluated in favor of chronic thromboembolic PHT, and one patient underwent endarterectomy (Figure 1).

Table 1. Demographics, symptoms, comorbidities, and risk factors.

	n
Age (mean±SD)	53.5±20.4
Male/Female, n	11/11
Symptoms	n (%)
Shortness of breath	22 (100)
Central chest and flank pain	18 (81.8)
Palpitation	16 (72.7)
Cough	15 (68.2)
Pain, redness, swelling in the leg	13 (59.1)
Wheezing	9 (40.9)
Producing sputum	2 (9.1)
Hemoptysis	1 (4.5)
Concomitant diseases and risk factors	n (%)
Immobilization	12 (54.5)
Hypertension	12 (54.5)
Deep vein thrombosis	10 (45.5)
Orthopedic surgery	6 (27.3)
Heart failure	6 (27)
Diabetes	5 (22.7)
Obesity	5 (22.7)
Cesarean section	4 (18.2)
Neurosurgery operation	1 (4.5)
Lymphoma	1 (4.5)
COVID-19	1 (4.5)
Breast carcinoma	1 (4.5)
Cerebrovascular disease	1 (4.5)

SD: standard deviation.

Table 2. Mean value of pulmonary artery pressure at 1-year follow-up of patients.

ECHO	PAP (mean±SD)
At hospitalization	53.0±13.6
At discharge from hospital	42.7±13.4
At month 1	37.6±12.6
At month 3	30.2±13.1
At month 6	25.4±10.1
At the end of 1 year	23.8±9.7

ECHO: Echocardiography; PAP: pulmonary artery pressure; SD: standard deviation.

DISCUSSION

When PTE is diagnosed, anticoagulant therapy should be started as soon as possible unless contraindications exist. In our study, the long-term outcomes of 22 patients diagnosed with submassive PTE and treated with UFH infusion were evaluated; accordingly, their PAP and D-dimer levels decreased significantly during follow-up, and PHT developed in three patients due to chronic PTE (CPTE).

Treatment of submassive PTE may be determined depending on the patient's clinical condition, drug contraindications, comorbidities, and hemodynamic findings. Although the role of systemic thrombolytic therapy is controversial, patients with clinical deterioration of submassive PTE are potential candidates for thrombolytic therapy[6]. A double-blind, randomized trial showed lower mortality with alteplase than with heparin alone in recurrent PTE, without the added risk of bleeding[7]. Another study comparing tenecteplase and heparin and examining 1,006 patients with submassive PTE reported less hemodynamic instability and mortality in the tenecteplase group[8]. The study by Rehman et al., which examined 86 patients with submassive pulmonary embolism, compared patients who received a

Figure 1. Endarterectomy tissues removed from pulmonary artery branches.

thrombolytic followed by a heparin infusion with those who received a heparin infusion alone and concluded that the PAP scores of patients who received an early thrombolytic followed by a heparin infusion decreased significantly[9]. Three-year follow-up data from the PEITHO trial showed no difference in long-term mortality or incidence of chronic thromboembolic PHT between the thrombolytic and heparin infusion groups[8].

The incidence of chronic thromboembolic PHT is 0.57% in the general population and 1.5% in patients with idiopathic PTE[1]. Factors predisposing to the development of PHT include recurrent venous thromboembolism and PTE of unknown cause. In our one-year follow-up, no recurrent PTE was detected. Thus, there was no case in which we could not detect the underlying risk factor. Nevertheless, 13.6% of chronic PHT were detected. PAP regressed significantly at one-year follow-up, and although the mean PAP of patients fell below 25 mmHg, this suggests that treatment with UFH does not prevent PHT development due to CPTE in submassive PTE. The main limitation of our study is the small number of patients and its descriptive study design. Studies on which treatment option prevents the development of CPTE in submassive PTE can be investigated with further case–control studies using larger patient collectives. Our descriptive study hypothesizes that UFH does not prevent the development of CPTE.

In a meta-analysis of 1,775 patients by Chatterjee et al., thrombolytic therapy was shown to be beneficial in reducing mortality, although it increased the risk of major bleeding (9.24%) and intracranial hemorrhage (ICH) (1.46%)[4]. Similarly, another meta-analysis by Riera-Mestre et al., which reviewed the outcomes of 1,833 patients, found that thrombolytic therapy reduced mortality despite the increased risk of major bleeding (5.9%) and ICH (1.74%)[5]. Although studies on the use of thrombolytics in the treatment of submassive PTE have been accelerated, there are few studies investigating the use of UFH, which reduces the risk of bleeding and has been used safely for many years, in submassive PTE and its long-term outcomes. In our study, none of the patients developed major bleeding or ICH.

Heparin-induced thrombocytopenia is a complication of PTE[10]. In our study, thrombocytopenia was not found in any of the cases. However, when comparing the initial PAP and PAP at the end of one year, we determined that the values decreased significantly in our cases. PAP was 20 mmHg or less in all, except in three patients. Although one case underwent endarterectomy for CPTE-related PHT, we did not detect any losses in our short- and long-term follow-up.

Post-PTE syndrome[11], which is defined in the literature as a long-term complication that causes functional losses after an acute PTE episode, including a decrease in the patient's quality of life during long-term follow-up, was not studied in our patients. This is another limitation of our study.

CONCLUSIONS

Our study suggests that UFH is safe in the treatment of submassive PTE in terms of bleeding risk and reduces PAP, but its impact on PHT development due to CPTE during long-term follow-up needs to be investigated in further case–control studies with larger patient populations.

AUTHORS' CONTRIBUTIONS

LÖ: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **BÖ:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **BA:** Formal Analysis.

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