Pulmonary embolism in patients with severe COVID-19 treated with intermediate- to full- dose enoxaparin: A retrospective study

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Key words: Pulmonary embolism; venous thromboembolism; COVID-19; enoxaparin; respiratory failure.

Highlights:
- Despite intermediate-to full-dose enoxaparin, 12 % of our patients developed PEs
- Among our patients who underwent CTPA, 50 % had confirmed PEs
- We hypothesize that our low PE prevalence may be due to enoxaparin treatment

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Abstract

Coronavirus disease (COVID-19) may predispose patients to pulmonary embolism (PE), despite standard thromboprophylaxis. Our retrospective study aimed to report the prevalence of PE in patients with COVID-19 and severe respiratory failure (SRF) treated with intermediate- to full-dose enoxaparin. We analyzed data from patients with COVID-19 pneumonia and SRF admitted to our Respiratory Intensive Care Unit (RICU) from February 27 to April 20, 2020. All patients received at least intermediate-dose enoxaparin (40 mg twice daily). Computed tomography pulmonary angiography (CTPA) was used to detect PE. Ninety-two patients with COVID-19 pneumonia and SRF were admitted to our RICU. Twenty-two patients underwent CTPA (24 %), 11 of whom had PEs (12%). We hypothesize that the enoxaparin treatment may be responsible for the lower prevalence of PE as compared to previous reports of similar patients, even if our report had several limitations, mainly the small sample size.

Introduction

In December 2019, a novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), quickly began to spread across Wuhan, China. It then triggered a global pandemic [1-4]. In February 2020, cases of coronavirus disease (COVID-19) began appearing abruptly in the Lombardy region of northwest Italy and quickly overwhelmed its healthcare system. By December 18, 2020, there are 1,921,778 patients diagnosed with COVID-19 in Italy with 67,8944 deaths [5].

Most patients with COVID-19 present with mild symptoms such as fever, cough, chills, muscle pain, and a loss of taste or smell. However, a significant proportion (10-29%) of hospitalized patients develop severe respiratory failure (SRF) and acute respiratory distress syndrome (ARDS) requiring admission to the intensive care unit (ICU) [1,2,5]. Venous thromboembolism

(VTE) is now recognized as one of the predominant cardiovascular hazards in patients with COVID-19 [6-11]. Recent studies report that patients with severe COVID-19 also often have coagulopathies with a predisposition for arterial and venous thromboembolisms, and therefore may benefit from anticoagulant therapy [6-10]. Recent studies have demonstrated a high prevalence of VTE in patients with COVID-19 admitted to ICU, particularly lower leg deep vein thromboses (DVTs) in 25% of 81 patients and pulmonary embolisms (PEs) in 20.6% of 107 patients [9-13]. The frequency of symptomatic VTE in patients in ICU with COVID-19 has been reported to be 27% [11].

Our study reports a case series of 92 patients with COVID-19 and SRF who were admitted to our respiratory intensive care unit (RICU) and who were treated with intermediate- or full-dose enoxaparin. The purpose of our study was to evaluate the prevalence of PE in patients with COVID-19 and SRF treated with intermediate- to full-dose enoxaparin.

Methods

Ninety-two patients diagnosed with COVID-19 and SRF [mean arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) <300 mm Hg] were admitted to our RICU for non-invasive positive-pressure ventilation (NIV) from February 27 to April 20, 2020.

Our RICU is a 15-bed ward with non-invasive cardiopulmonary monitoring and a non-invasive mechanical ventilator designated to each bed. This unit provides 600 minutes of nursing care per bed. It is staffed by three pulmonologists from 8 AM to 8 PM, one pulmonologist from 8 PM to 8 AM on workdays, and one pulmonologist on public holidays.

All patients were diagnosed with COVID-19 based on the World Health Organization guidelines [14]. Emerging data suggested an increased prevalence of VTE among critically ill patients with COVID-19 [6,10,12], despite having undergone standard thromboprophylaxis. Therefore, we treated these patients with intermediate- to full-dose enoxaparin. Patients were generally treated with intermediate- dose enoxaparin (40 mg twice daily). However, if their D-dimer levels were higher than 3000 ng/mL and/or if they experienced an acute worsening of their respiratory or hemodynamic status, they were treated with full-dose enoxaparin (1 mg/kg of body weight twice daily). Patients with renal failure were treated with adjusted doses of enoxaparin based on their anti-Xa activity. After PEs were diagnosed, patients were treated with full-dose enoxaparin.

Patients with D-dimer levels >3000 ng/mL and/or acute worsening of their respiratory or hemodynamic status underwent computed tomography pulmonary angiography (CTPA) to confirm or exclude PE. If a patient's clinical status did not allow for a safe transfer to the radiology department (*e.g.*, they were dependent on NIV), the patient was treated with full-dose enoxaparin. The choice to use intermediate- or full-dose enoxaparin was always made in consideration of the patient's risk for bleeding [15]. The clinical characteristics, adverse events probably related to enoxaparin therapy [thrombocytopenia (*i.e.*, platelet level <50,000/μL), hematomas, bleeding requiring transfusion of two or more units of concentrated red blood cells], and outcomes of these consecutive patients with COVID-19 were retrospectively analyzed. This study was approved by the Valpadana ATS ethics committee (Cremona, Italy) on July 7, 2020. The study code is 95-2020-OSS_FARMMN30).

Informed consent was waived due to the emergency situation regarding COVID-19 at the time.

Statistical analysis

The association between categorical variables was evaluated using Pearson's chi-square test. Statistical comparisons for continuous variables were conducted using the unpaired Student's *t*-test. All tests were two-tailed, and p-values of <0.05 were considered statistically significant. The analysis was conducted using the Statistical Package for Social Sciences, version 23 (Armonk, New York, NY, USA).

Results

Ninety-two patients with diagnosed COVID-19 were admitted to our RICU between February 27 and April 20, 2020. Twenty-two (24 %) patients underwent CTPA-PEs were confirmed in 11 (12%) of these patients. Table 1 shows the characteristics and clinical course of all the included patients.

The mean age of the patients was 58±11 years (range 28-85 years); and 21 (22.8%) patients were female. Obesity was significantly prevalent (45% of patients), and the most common comorbidities were hypertension (46%) and diabetes mellitus (19%).

The patients had SRF (mean PaO_2/FiO_2 of 143±45 mm Hg) and high D-dimer levels (the mean D- dimer level was 2698±2673 ng/mL). The mean PaO_2/FiO_2 was 122± 47 mm Hg in patients who died and 146±44 mm Hg in patients who survived (p=0.10).

Ten (11%) patients developed adverse events [three patients had intramuscular hematomas, two had thrombocytopenia (*i.e.*, platelet level <50,000/μL), and five had bleeding requiring the transfusion of two or more units of concentrated red blood cells], eight of whom were treated with full-dose and two with intermediate-dose enoxaparin. None of these 10 patients died. Enoxaparin was discontinued in four patients and was temporarily reduced in six patients.

Eleven (12%) patients died in hospital. The mean age of the deceased patients was statistically different from that of the surviving patients (70±9 years *vs* 56±11 years, respectively; p<0.0001). No statistically significant difference in hospital mortality was found between patients with and without PE (p=0.90). Table 2 shows the characteristics of patients with COVID-19 with and without PE.

The mean PaO_2/FiO_2 was 133±47 mm Hg in patients with PE and 144±45 mm Hg in patients without PE (p=0.46). The mean D-dimer level was 4582±4424 ng/mL in patients with PE and 2634±2529 ng/mL in patients without PE (p=0.20). Moreover, the body mass index (BMI) was greater than 30 kg/m^2 in five (45%) patients with PE and in 40 (49%) patients without PE.

Discussion

Pulmonary embolism was diagnosed in 11 (12%) patients admitted to our RICU for COVID-19 pneumonia and SRF, despite treatment with intermediate- to full-dose enoxaparin. However, the frequency of PE in our patient population was lower than that previously reported in similar patients [12]. Although our study prob-

ably underestimated the real frequency of PE, because only a small portion (24%) of patients underwent CTPA, it is possible to assume that the reduced PE incidence may have been due to the use of a higher-than-prophylactic dose of enoxaparin.

The frequency of VTE is highest in the ICU setting and has ranged from 25%, when symptomatic disease is considered, to 69%, when surveillance venous ultrasonography is performed [6,9,10-13].

Our patients underwent CTPA only if there was a clinical suspicion of PE and/or in the presence of elevated D-dimer levels, and if a patient's clinical status allowed for a safe transfer to the radiology department. Considering these assumptions, 50% of our patients who underwent CTPA had confirmed PEs.

Pneumonia in patients with COVID-19 can lead to sepsis and the release of inflammatory cytokines, including interleukin (IL)-6, IL-8, and tumor necrosis factor-a [16]. Inflammatory cytokines can promote blood coagulation in various manners [10]. The reported incidence of disseminated intravascular coagulation (DIC) in patients who have died from COVID-19 pneumonia is 74% [6]. A high prevalence of *in situ* micro-thrombosis, suspected to be due to endothelial injury from direct viral infection, has also been described [17-19]. Inflammation, DIC, hypoxemia, obesity, and immobility may predispose patients with COVID-19 and SRF to the development of thromboembolic complications [1-4,12,20].

Emerging data suggest an increase in the prevalence of VTE among patients with COVID-19, especially among patients with more severe disease [10,12].

To our knowledge, this study is the first to analyze data from patients with COVID-19 admitted to the RICU for non-invasive mechanical ventilation. Due to the small number of patients with PEs, we did not identify any statistically significant differences in hospital mortality, D-dimer levels, or PaO_2/FiO_2 between patients with and without PE. However, we identified a trend toward a higher D-dimer level and lower PaO_2/FiO_2 in patients with PEs. An elevated D-dimer level is a sign of excessive activation of coagulation and hyperfibrinolysis. Thus, D-dimer levels are often used to detect the presence of an active thrombus. The D-dimer level has high sensitivity but low specificity [10].

The D-dimer cut-off value of 3000 ng/mL has a sensitivity, specificity, and negative predictive value for PE of 76.9 %, 94.9 %, and 92.5 %, respectively [10].

Patients admitted to our RICU had SRF with moderate to severe ARDS [21]. It has recently been reported that the presence of ARDS has the strongest association with adverse outcomes, including major arterial or venous thromboembolism, symptomatic VTE, and death [11]. Moreover, 72% of our patients had elevated D-dimer levels (*i.e.*, >1000 ng/mL) and approximately one-third of patients had very elevated D-dimer levels (*i.e.*, >3000 ng/mL). The prevalence of obesity (49%) among our patients may have contributed to the increased frequency of PE, which has also been reported by other authors [12,21]. The aforementioned characteristics of our patients indicated that they had a very high thromboembolic risk. As suggested by some authors and scientific societies, we used a higher-than- prophylactic dose of enoxaparin [10,12,20,22,23].

Our report had several limitations. First, this was a retrospective, single-center study with a small sample size. Second, our study probably underestimated the actual frequency of PE because only a small portion (24%) of patients underwent CTPA, which is the gold standard for PE diagnosis [24]. Third, it was impossible to exclude the presence of PE at the time of admission and, thus, before starting treatment with enoxaparin.

Table 1. Characteristics of 92 patients with COVID-19 upon admission to the respiratory intensive care unit and during their hospital course.

Characteristic	Results
Age (y)	58 (11)
Female patients	21 (22%)
BMI >30 kg/m^2	42 (45%)
Hypertension	43 (46%)
Diabetes	18 (19%)
PaO_2/FiO_2 (mm Hg)	143 (45)
200 mm Hg < PaO_2/FiO_2 ≤300 mm Hg	11 (12%)
100 mm Hg < PaO_2/FiO_2 ≤200 mm Hg	67 (73%)
PaO_2/FiO_2 <100 mm Hg	14 (15%)
D-dimer level (ng/mL)	2698 (2673)
D-dimer level ≤1000 ng/mL	26 (28%)
1000 ng/mL <D-dimer level ≤3000 ng/mL	34 (37%)
D-dimer level >3000 ng/mL	32 (35%)
Lactate dehydrogenase level (U/L)	765 (323)
Fibrinogen level (mg/dL)	636 (168)
Patients who underwent CTPA	22 (24%)
Pulmonary embolism diagnosed via CTPA	11 (12%)
Enoxaparin-related adverse effects	10 (11%)
Patients who died in hospital	11 (12%)
Mean age of patients who died (y)	70 (9)*
Mean age of patients who survived (y)	56 (11)*

The data are presented as number (%) or mean (standard deviation); BMI, body mass index; CTPA, computed tomography pulmonary angiography; PaO2/FiO2, mean arterial oxygen partial pressure/fractional inspired oxygen; *p<0.0001.

Table 2. Characteristics of patients with COVID-19 with and without pulmonary embolism.

Characteristic	Patients with PE	Patients without PE	p-value*
Age (y)	58 (13)	58 (11)	0.92
BMI >30 kg/m^2	5 (45%)	40 (49%)	0.52
PaO_2/FiO_2	133 (47)	144 (45)	0.46
D-dimer level (ng/mL)	4582 (4424)	2634 (2529)	0.20
LDH level (U/L)	900 (412)	745 (308)	0.15
Ferritin level (ng/mL)	1687 (1432)	2102 (2289)	0.56
Hospital mortality	1 (9%)	10 (12%)	0.90

The data are presented as numbers (%) or as means (standard deviation); PE, pulmonary embolism, BMI, body mass index; LDH lactate dehydrogenase; *p-value <0.05 is statistically significant.

In conclusion, to the best of our knowledge, this study is the first to report the incidence of PE among patients with severe COVID-19 who were treated with intermediate- to full-dose enoxaparin. Pulmonary embolism was diagnosed in 12% of our patients, despite the treatment dose. However, the optimal thromboprophylactic regimen in this patient population remains unknown [20,23,25]. Well- designed, randomized-controlled trials are needed to analyze the risk-benefit ratio of more aggressive low-molecular-weight thromboprophylaxis in these patients [20,23]. A number of randomized controlled trials have been developed to evaluate the risks and benefits of anticoagulation treatment in patients with COVID-19 (visit ClinicalTrials.gov for the current list of trials) [25]. The results of these trials should shed light on the current doubts regarding this important clinical issue.

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