Pulmonary embolism in patients with severe COVID-19 treated with intermediate- to full-dose enoxaparin

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Research Article

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Abstract

Background: Coronavirus disease 2019 (COVID-19) may predispose patients to venous thromboembolism (VTE) due to inflammation, hypoxia, immobilization, and diffuse intravascular coagulation, despite standard thromboprophylaxis. Our retrospective study reports the incidence of pulmonary embolism (PE) in patients with COVID-19 and severe respiratory failure(SRF) treated with intermediate to full-dose enoxaparin. .

Methods: This retrospective case series analysed data from patients with COVID-19 pneumonia and severe respiratory failure (SRF) admitted to our Respiratory Intensive Care Unit (RICU) between February 27 and April 20, 2020 for non-invasive positive-pressure ventilation. All patients received at least intermediate-dose enoxaparin (40 mg twice daily). If PE was suspected or diagnosed, patients were treated with full-dose enoxaparin (1 mg/kg twice daily). Computed tomography pulmonary angiography (CTPA) was used to detect PE in patients with elevated D-dimer levels (> 3000 ng/mL) and/or other clinical indicators, including sudden worsening of cardiopulmonary status.

Results: Ninety-two patients (71 males, 21 females; mean age 58 ± 11 years) with COVID-19 pneumonia and SRF (mean arterial oxygen partial pressure/fractional inspired oxygen [PaO2/FiO2] of 143 ± 45 mm Hg) were admitted to our RICU. Twenty-two patients underwent CTPA (24%), with PEs detected in 11 (12%). Mean PaO2/FiO2 and mean D-dimer levels did not significantly differ between patients with or without PE. Eleven patients (12%) died in the hospital, with a mean age of 70 ± 11 years for deceased patients and 56 ± 11 years for surviving patients ($p < 0.0001$).

Conclusions: PE was diagnosed in 12% of patients despite intermediate to full-dose enoxaparin treatment. However the incidence of PE in our patients was lower than that previously reported. We hypothesize that this reduced PE incidence may have been secondary to the higher than prophylactic enoxaparin dose that was used.

Introduction

In December 2019, a novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), quickly began to spread in Wuhan, China. It triggered a global pandemic [1-4].

In February 2020, cases of coronavirus disease 2019 (COVID-19) abruptly began appearing in the Lombardy region of northwest Italy and quickly overwhelmed its healthcare system. By April 20, 2020, 181,228 patients were diagnosed with COVID-19 in Italy and 24,114 deaths occurred [5].

Most patients with COVID-19 present with mild symptoms such as fever, cough, chills, muscle pain, and a new loss of taste or smell. However, a significant proportion (10%–29%) of hospitalised patients develops severe respiratory failure (SRF) and acute respiratory distress syndrome (ARDS) necessitating intensive care unit (ICU) admission [1, 2, 5]. Recent studies [6-10] report that patients with severe COVID-19 disease also often have coagulopathies with a predisposition for arterial and venous thromboembolisms and

may benefit from anticoagulant therapy. Recent studies [9-11] have demonstrated lower leg deep vein thromboses (DVTs) in 25% of 81 COVID-19 ICU patients and pulmonary embolisms (PEs) in 20.6% of 107 COVID-19 ICU patients.

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

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 noninvasive positive-pressure ventilation (NIV) from February 27, 2020 to April 20, 2020.

Our RICU is a 15-bed ward with noninvasive cardiopulmonary monitoring and a noninvasive mechanical ventilator for each bed. This unit provides 600 minutes of nursing care per bed and is staffed by three pulmonologists from 8 am to 8 pm and by one pulmonologist from 8 pm to 8 am on workdays and by one pulmonologist on holidays.

All patients were diagnosed with COVID-19, based on the World Health Organization guidelines [12]. Emerging data suggested an increased prevalence of venous thromboembolism (VTE) among critically ill COVID-19 patients, [6,10-11], despite their 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 statuses underwent computed tomography pulmonary angiography (CTPA) to confirm or to 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 with consideration of the patient's bleeding risk [13].

Clinical characteristics, adverse events probably related to enoxaparine therapy(thrombocytopenia[i.e. platelet level, <50,000/μL], haematomas, bleeding necessitating the transfusion of two or more units of concentrated red blood cells) and outcomes of these consecutive COVID-19 patients were retrospectively analysed.

This study was approved by the Valpadana ATS ethics committee (Cremona, Italy) on July 07, 2020. The study code is 95-2020-OSS_FARM-MN30).

Statistical analysis

Associations between categorical variables were evaluated using the Pearson's chi-squared test. Statistical comparisons for continuous variables were conducted by using the unpaired Student's *t*-test. All tests were two-tailed, and values of $p < 0.05$ were 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, 2020 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 hospital course of all patients.

Table 1. Characteristics of 92 patients with COVID-19 on 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 < $PaO_2/FiO_2 \leq$ 300 mm Hg	11 (12%)
100 mm Hg < $PaO_2/FiO_2 \leq$ 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 the 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 the number (%) or as the mean (standard deviation)..

COVID-19 coronavirus disease 2019, *BMI* body mass index, *CTPA* computed tomography pulmonary angiography, *PaO_2/FiO_2* mean arterial oxygen partial pressure/fractional inspired oxygen

*The *p*-value is < 0.0001

The mean age of 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 frequent 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—eight of whom were treated with full-dose enoxaparin and two of whom were treated with intermediate-dose enoxaparin—developed adverse events (three patients had intramuscular haematomas, two patients had thrombocytopenia [i.e. platelet level, <50,000/μL], and five patients had bleeding necessitating the transfusion of two or more units of concentrated red blood cells). None of these 10 patients died. Enoxaparin was stopped in four patients and temporarily reduced in six patients.

Eleven (12%) patients died in the hospital. The mean age of deceased patients was statistically different from that of surviving patients (70 ± 9 years vs. 56 ± 11 years, respectively; $p < 0.0001$).

We did not find statistical differences in hospital mortality between patients with and without PE ($p = 0.90$). Table 2 shows the characteristics of COVID-19 patients with and without PE.

Table 2. Characteristics of COVID-19 patients 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 the number (%) or as the mean (standard deviation)

COVID-19 coronavirus disease 2019, PE pulmonary embolism, SD standard deviation, BMI body mass index, LDH lactic dehydrogenase, PaO_2/FiO_2 mean arterial oxygen partial pressure/fractional inspired oxygen

* A *p*-value < 0.05 is statistically significant

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 their being treated with intermediate- to full-dose enoxaparin. The incidence of PE in our patient population was lower than the incidence previously reported in COVID-19 patients [11]. We hypothesise that this reduced PE incidence may have been secondary to using a higher-than-prophylactic dose of enoxaparin.

Pneumonia in COVID-19 patients can lead to sepsis and to the release of inflammatory cytokines, including interleukin (IL)-6, IL-8, and tumour necrosis factor-α [15]. 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]. Inflammation, DIC, hypoxemia, obesity, and immobility may all predispose patients with COVID-19 and SRF to the development of thromboembolic complications [1–4, 11, 14].

Profound coagulopathy associated with COVID-19 was first described soon after the start of the pandemic; however, several studies and a state-of-the-art review related to clinical VTE have been reported [1,6,7,9–11,14]. Emerging data suggest an increased prevalence of VTE among patients with COVID-19, especially among patients with more severe disease. In particular, one study reported lower leg DVTs in 25% of 81 ICU patients with COVID-10, and another study found PEs in 20.6% of 107 ICU patients with COVID-19 [10-11].

To our knowledge, this study is the first to analyse data from COVID-19 patients hospitalised in an RICU for non-invasive mechanical ventilation . Owing 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. We did, however, identify a trend toward higher D-dimer levels and lower PaO_2/FiO_2s 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 values for PE of 76.9%, 94.9% and 92.5%, respectively [10].

Patients admitted to our RICU had SRF and moderate to severe ARDS [16]. Moreover, 72% of these 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 an increased PE frequency, which has been reported by other authors [11, 17]. The aforementioned characteristics of our patients indicated they had a very high thromboembolic risk. As

suggested by some scientific societies, we used a higher-than-prophylactic dose of enoxaparin [10, 11, 14, 17, 19].

Our report had several limitations. It was a retrospective, single-centre study with a small sample size. Only a small proportion (24%) of patients underwent CTPA, which is the gold standard for PE diagnosis [18].

In conclusion, to 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. The prevalence of VTE is high among severe COVID-19 patients. However, the optimal thromboprophylactic regimen in this patient population remains unknown [14, 19]. Well-designed, randomised-controlled trials analysing more aggressive low-molecular-weight thromboprophylaxis are sorely needed to guide better risk stratification and guide the clinical management of these patients [14, 19].

Declarations

Funding (Not applicable)

Conflicts of interest/Competing interests (Not applicable)

Availability of data and material (Data are available upon a reasonable request to the corresponding author. No additional data available)

Code availability ('Not applicable')

Ethics approval: This study was approved by the Valpadana ATS (Cremona – Italy) ethics committee on 07/07/2020 (Study code 95-2020-OSS_FARM-MN30).

Consent to participate ((Not applicable)

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