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Venous thrombotic events in severe and critically COVID-19 patients despite high dose prophylactic low-molecular-weight heparin

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ABSTRACT

Hypercoagulation is one of the most distinct prognostic factors of patients with COVID-19 and has been associated with arterial thrombosis and other venous thrombotic events (VTE). Bleeding complications are far less encountered. The International Society on Thrombosis and Haemostasis (ISTH) guidance advises giving prophylactic low-molecular-weight heparin (LMWH) to prevent these events, although there is evidence that the incidence remains high despite using prophylactic LMWH. We describe three cases of COVID-19 pneumonia that were admitted to our intensive care unit (ICU) and developed acute pulmonary embolisms (APE) despite high dosage prophylactic LMWH. These cases raise concerns about using prophylactic LMWH instead of therapeutic anticoagulation in severe and critically COVID-19 patients.

1. Introduction

Several studies have shown that severe and critically COVID-19 patients exhibit a so-called hypercoagulable state, which is one of the most distinct prognostic factors of poor outcome in severe COVID-19 patients [1,2]. It is associated with thrombotic events while bleeding complications are far less encountered [3]. In a recently published article [4], the cumulative incidence of arterial and venous thrombotic events in COVID-19 patients admitted to three Dutch ICU’s was analyzed. This incidence was remarkably high despite the use of prophylactic LMWH. Likewise, Llitjos et al. [5] observed a cumulative incidence of 100% of VTE in the group treated with prophylactic LMWH when screened systematically by ultrasound. Still, the ISTH guidance [6] advises giving only prophylactic LMWH, despite this remarkably high incidence of VTE under prophylactic LMWH. In this article, we will describe three cases who were admitted to the ICU of our teaching hospital in The Netherlands and developed VTE despite high prophylactic LMWH. The three cases presented themselves all in the early stage of the COVID-19 pandemic. In this period, there was no systematic screening of VTE in place, and radiology images were only requested when there was a clinical suspicion of thrombotic complications. Furthermore, our hospital protocol of anticoagulation prophylaxis depended on the severity of the COVID-19 infection. In the ICU, patients received therapeutic anticoagulation, while patients in the general ward received weight-adjusted high prophylactic dalteparin. We present these three cases to increase the understanding of the hypercoagulable state in COVID-19 patients and to reconsider the use of prophylactic LMWH as a preventive measure in severe and critically COVID-19 patients.

2. Results

The first case is a 27-year-old woman, with a history of asthma, who presented herself with a week of cough, dyspnea, and fever. On presentation, she was in respiratory distress despite administration of high flow oxygen (15L/min). Laboratory findings revealed a CRP of 135 mg/L, D-dimer of 0.64 mg/L, PT of 11.0 seconds, and platelets of 332109/L. The chest X-ray showed bilateral consolidations. She tested positive for SARS-CoV-2. Due to the persisting hypoxemia, she was intubated and received, according to our hospital ICU protocol, weight-adjusted therapeutic LMWH as a preventive measure. Cefotaxime was given for four days as selective decontamination of the digestive tract (SDD). She was treated with ciprofloxacin for two days until the urinary antigen test for legionella was negative. After six days, the patient could be extubated and transferred to the ward. As there was no clinical suspicion of VTE at
presentation, it was decided to convert the therapeutic dosage to weight-adjusted high prophylactic LMWH, dalteparin 7500IE, according to our hospital protocol for general wards. Thereafter, she developed progressive dyspnea which was due to lobar and segmental APE. She received therapeutic anticoagulation and improved clinically. As no ultrasound was made at presentation or during admission, it is not possible to differentiate whether the APE developed due to a deep vein thrombosis already present at admission. She was discharged with a direct oral anticoagulant (DOAC).

The second case is a 53-year-old woman with no medical history. She presented herself with ten days of coughing, fever, and progressive dyspnea. She weighed 95 kg. She demonstrated respiratory distress despite high-flow oxygen. The CRP was 143 mg/L, the D-dimer 0.72 mg/L, the PT 11.4 seconds, and the platelets 24010^9/L. Chest X-ray revealed bilateral consolidations and the SARS-CoV-2 PCR was positive. She was admitted to the ICU and intubated for five days. Cefotaxime, in the context of SDD and ciprofloxacin were given for five days. She received dalteparin 7.500IE twice daily as a preventive measure. This dosage was subtherapeutic due to her weight. After extubation, her clinical recovery stagnated and the d-dimer increased to 12.10 mg/L. The obtained CT scan showed central and segmental pulmonary embolisms. The dosage of dalteparin was increased, and she started to recover. She could be discharged with a DOAC.

A 60-year-old man with a history of diabetes, myocardial infarction, and obstructive sleep apnea syndrome, presented himself with a week of fever and coughing. On presentation, he needed medium-flow oxygen (5L/min) via nasal cannula to reach a SpO2 of 97%. The CRP was 26 mg/L, the D-dimer 1.46 mg/L, and platelets were 12810^10/L. The chest X-ray showed bilateral consolidations. The SARS-CoV-2 PCR was positive. He was admitted to the ward and received cefuroxime, azithromycin, hydroxychloroquine, and weight-adjusted high prophylactic dalteparin.

On day two of admission, he developed respiratory distress and needed intubation. He was admitted to the ICU, and the antibiotics were changed to cefotaxime, as SDD, and ciprofloxacin. The ciprofloxacin was stopped after the urine antigen test for legionella was negative. The dalteparin was increased to weight-adjusted therapeutic LMWH and was monitored using anti-Xa levels ranging from 0.6 to 1.0 u/mL. The first anti-Xa level was subtherapeutic with 0.2 u/mL. It was decided to increase the dosage of dalteparin, resulting in anti-Xa levels of 0.9 u/mL.

On day 8, an APE was suspected due to an increase in respiratory distress, but the obtained CTa scan did not show one. On day 14, an infected thrombus was suspected as he had an ongoing fever and the blood cultures showed coagulase-negative Staphylococci despite a recent change of the central venous catheter. Although no thrombus was seen adherent to the previous removed one, an ultrasound was obtained. The ultrasound showed a thrombus in the right jugular vein, but none was detected in the lower and upper extremities. A CTa scan was made which revealed lobar and segmental APE. Since the patient developed VTE while having therapeutic anti-Xa levels, it was decided to start argatroban, a direct thrombin inhibitor. He began to recover and could be extubated and transmitted to the ward.

3. Discussion

In summary, we described three critically COVID-19 patients admitted to our hospital who developed VTE despite receiving high levels of preventative anticoagulation. This observation underlines the hypercoagulable state of COVID-19 and raises concerns about the use of prophylactic LMWH as a sufficient preventative measure in severe and critically COVID-19 patients. As mentioned, we used two different protocols based on the severity of COVID-19. We admitted 338 patients, of which 78 were admitted to the ICU, from March till August. In total, 24 patients (7.10%) were diagnosed with thrombotic complications, consisting of 22 APE, one arterial thrombosis, two sinus thrombosis, and four jugular thrombosis. Five patients developed thrombotic complications receiving preventative therapeutic anticoagulation.

Several studies have shown a more pronounced hypercoagulable state in critically COVID-19 patients compared to mild patients [1,2]. In mild hospitalized COVID-19 patients, the development of hypercoagulation could be a prognostic feature, and monitoring coagulation marks is essential. High-clinical awareness of thrombotic complications is advised [6]. When these safeguards are in place, prophylactic LMWH should be sufficient as a preventative measure. In severe and critically COVID-19 patients, thrombotic complications are frequently seen despite the use of prophylactic LMWH [4,5]. The cumulative incidence increases to 100% when these patients are screened systematically using ultrasound [5].

It could be hypothesized that the thrombotic complications, seen in severe and critically COVID-19, despite the use of prophylactic LMWH, are due to the interplay between inflammation and coagulation [7,8]. COVID-19 evasion causes a cytokine storm in severe and critically patients, resulting in an upregulation of several cytokines, which promotes endothelial damage, the release of tissue factor and fibrinogen synthesis [8,9]. It also stimulates a key player in the innate immunity, the neutrophil, which can trigger the coagulation by producing extracellular neutrophil traps (NETs). These traps induce cell death, intravascular thrombosis, and further release of inflammatory products [10]. Therefore, uncontrolled production of NETs will activate and amplify inflammation and thrombosis [7,10].

This vicious cycle of immune-thrombosis can result in the formation of arterial thrombosis, VTE, and micro-vascular thrombi eventually leading to hypoxia and respiratory decline seen in severe and critically COVID-19 patients [7,8]. It is essential to interfere in this cycle to prevent further endothelial damage, respiratory decline, and even death. Therapies such as IL-1 and IL-6 antagonists could decrease the cytokine storm and may prevent thrombotic complications [7]. In addition, LMWH should be given as it has immunomodulatory effects, and will prevent an acceleration of the immune system due to limiting thrombotic complications [9]. However, the high fibrin levels exhibited by COVID-19 patients makes them more resistant to LMWH [8]. Thus, prophylactic LMWH is likely to be insufficient as a preventative measure of thrombotic complications. As the cumulative incidence of VTE in severe and critically COVID-19 patients is high, and bleeding is rarely seen, it could be justifiable to use therapeutic anticoagulation in combination with anti-inflammatory drugs.

The primary purpose of this case series was to question the advice of prescribing only prophylactic LMWH dosage in severe and critically COVID-19 patients. The use of therapeutic coagulation as a preventative measure of thrombotic complications should be evaluated and confirmed by randomized controlled trials. In the absence of this evidence, we need to balance the possibility of giving insufficient prevention while using prophylactic LMWH with the risks of therapeutic anticoagulation.

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Declaration of competing interest

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