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Enhanced thromboprophylaxis in critically ill patients with COVID-19 infection

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ABSTRACT

Background: Patients with severe SARS-CoV-2 infection have been shown to have abnormal coagulation parameters and are at increased risk of thromboembolism. The optimal thromboprophylaxis regimen that minimizes thrombosis without increased risk of serious bleeding is uncertain.

Objectives: To describe the efficacy and safety of increased intensity (enhanced) thromboprophylaxis in patients with COVID-19 admitted to the medical intensive care unit (MICU).

Methods: This is a retrospective cohort analysis of patients with a diagnosis of COVID-19 admitted to the MICU of an urban safety net hospital. With the exception of patients being supported with extracorporeal membrane oxygenation or on chronic anticoagulation who received therapeutic dosing of anticoagulation, thromboprophylaxis was given as either enoxaparin or unfractionated heparin in doses higher than those recommended for standard prophylaxis, but lower than those used for therapeutic anticoagulation.

Main results: Of the 120 patients managed with an enhanced thromboprophylaxis protocol, 6 (5%) experienced thromboembolism as a result of their COVID-19 disease (1 pulmonary embolus, 4 deep vein thromboses, and 1 arterial embolism). Four patients experienced major bleeding while receiving therapeutic anticoagulation.

Conclusions: In critically ill patients with COVID-19, increased intensity (enhanced) thromboprophylaxis appears to be effective at preventing clinically significant thromboembolic events without an increased risk of serious bleeding.

1. Introduction

In late December 2019 the SARS-CoV-2 coronavirus was identified as the causative agent of a severe viral pneumonia that emerged in Hubei Province, China and spread globally, causing the COVID-19 pandemic [1]. Early in the pandemic it was recognized that patients hospitalized with COVID-19 had abnormal coagulation parameters and were at increased risk for thromboembolic complications [2–4]. A report from Wuhan found that abnormal coagulation parameters, especially a markedly elevated D-dimer, were associated with a significantly increased risk of mortality [2]. The same authors reported that patients with a greater than 6-fold elevation in D-dimer and high sepsis coagulopathy score had lower mortality if they had been given prophylactic doses of low molecular weight heparin instead of no prophylaxis [3]. Subsequently, reports from Europe found an unexpectedly high incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) when COVID-19 patients received standard prophylaxis with unfractionated or a low molecular weight heparin [4,5]. A study from the Netherlands of 184 critically ill patients with COVID-19 reported a cumulative incidence of thromboembolism of 31% despite treatment with standard prophylaxis [4]. Similarly, a French multicenter study documented pulmonary embolism in 25 of 150 (16.7%) patients with COVID-19 ARDS despite universal use of prophylactic or therapeutic anticoagulation, an incidence that was 10-fold higher than was observed in non-COVID-19 ARDS [5]. Besides DVT and PE, additional reported thrombotic complications of COVID-19 have included excessive clotting of continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) filters and arterial thromboses causing stroke, myocardial infarction or limb ischemia [5].

Although the heightened risk of thrombosis in COVID-19 is not in question, the optimal method of prevention remains controversial. A retrospective study of COVID-19 patients undergoing mechanical...
ventilation reported a lower mortality when anticoagulation was given in therapeutic rather than prophylactic doses, prompting the authors to recommend therapeutic anticoagulation for critically ill patients with COVID-19 [6]. However, others have questioned this approach due in part to the increased bleeding risk with therapeutic anticoagulation [7] and current guidelines recommend use of standard prophylaxis in the absence of a defined thrombotic event [8]. Ongoing randomized trials will hopefully better define the optimal anticoagulation strategy, but in the meantime clinicians must balance the perceived risks of thrombosis and bleeding when ordering anticoagulation for patients with COVID-19.

An alternative to either standard prophylaxis or therapeutic anticoagulation employs an intermediate dosing strategy [9]. With this enhanced prophylactic regimen the dose of low molecular weight or unfractionated heparin is increased but remains below levels used for therapeutic dosing. In the absence of evidence supporting a definitive approach, our institution elected to use enhanced prophylaxis as the default approach for hospitalized patients with COVID-19. In the current study we report our experience with this method of prophylaxis in critically ill COVID-19 patients admitted to our MICU.

2. Methods

We performed a retrospective analysis of patients with a PCR-confirmed diagnosis of COVID-19 who were admitted to the MICU of Hennepin County Medical Center between April 24th 2020 and August 26th 2020. Our study was approved by the IRB and the need for written consent was waived since patient data was de-identified.

Patients were managed with a thromboprophylaxis regimen that was adapted from the strategy proposed by Moll (Supplemental Fig. 1) [9]. Enoxaparin was our agent of choice unless the creatinine clearance was less than 30 mL/min, in which case the patient received unfractionated heparin. For patients with a D-Dimer level <2500 ng/mL (10 x upper limit of normal), enoxaparin or unfractionated heparin was dosed on the basis of BMI. If the D-dimer was >2500 ng/mL, patients received either weight-based enoxaparin (0.5 mg/kg twice daily) or a heparin infusion targeted to a sub-therapeutic anti-Xa goal of 0.3–0.5 IU/mL. Therapeutic dosing of heparin or enoxaparin was limited to patients who were on chronic anticoagulation at baseline or were being supported with extracorporeal membrane oxygenation (ECMO).

Thromboembolic events were investigated on the basis of clinical suspicion. Screening for DVT or PE was not utilized. For purposes of this study, we included venous and arterial thrombotic events diagnosed with imaging (CT angiogram, doppler ultrasound or MRI) and determined by the authors to be a consequence of COVID-19 infection. We did not include isolated catheter-associated thromboses, superficial vein thromboses, or continuous renal replacement therapy (CRRT) filter or extracorporeal membrane oxygenation (ECMO) filter clots. Major bleeding was defined as either an acute change in hemoglobin of at least 2 g/dL or transfusion of at least 2 units of packed red blood cells related to bleeding, or any intracranial hemorrhage [10].

3. Results

The study population included 126 patients with COVID-19 who were admitted to our MICU during the four-month study period. The median age was 61.5 (range 20–88) years, 81 (68%) were male, and their median BMI was 29.6 (range 16.2–63.2). The most common medical comorbidity was hypertension (58%), followed by diabetes mellitus (42%) and chronic respiratory disease (15%). Ninety-five (79%) were mechanically ventilated, 82 (68%) were diagnosed with ARDS and 42 (35%) died within the study period due to causes related to their COVID-19 infection. Additional patient characteristics are shown in Supplemental Table 1. Six patients did not receive chemical thromboprophylaxis because of active bleeding or significant thrombocytopenia (platelet count <50,000/μL).

Of the remaining 120 patients who received chemical thromboprophylaxis according to our protocol, the dose was high intensity for 12, moderate intensity for 40, and low intensity for 68, respectively (Supplemental Fig. 1).

Six patients experienced a thromboembolic event, including 1 with PE, 4 with DVT and 1 who developed multiple small foci on brain MRI consistent with cerebral emboli and a splenic infarct (Table 1). Events occurred at a median of 13.5 days (range, 3–31 days) from hospital admission. At the time the thromboembolic event was diagnosed, 2 patients were on the low intensity regimen, 3 were on the moderate intensity regimen, and 1 was on therapeutic heparin. Three of the 6 patients died, but in no case was the thromboembolic event felt to be a major contributor to death. A summary of thrombotic and bleeding events based on antithrombotic regimen is depicted in Fig. 1.

Four patients experienced major bleeding while receiving therapeutic anticoagulation despite having anti-Xa values in the target range at the time of bleeding. One patient being supported with ECMO had a catastrophic intracranial hemorrhage while on therapeutic heparin. A second ECMO patient had developed a DVT while on therapeutic heparin and was receiving therapeutic enoxaparin when he had a massive retroperitoneal hemorrhage with resultant intra-abdominal hypertension, necessitating laparotomy. The remaining two cases occurred in association with therapeutic heparin for ECMO and manifested as bleeding from the tracheobronchial tree and significant oozing at cannula insertion sites.

4. Discussion

The principal finding of this study is that only 6 of 120 (5%) patients admitted to the ICU with COVID-19 had a clinically significant thromboembolic event while being managed with an enhanced thromboprophylaxis protocol devised by Moll [9]. This incidence of DVT and PE was significantly lower than previously reported when critically ill patients with COVID-19 were managed with standard dose prophylaxis [4,5]. In addition, use of more intense prophylaxis was not associated with any serious bleeding events. Major bleeding, including a fatal intracranial hemorrhage, was limited to patients who were receiving therapeutic anticoagulation.

A previous retrospective study examined the impact of higher intensity prophylaxis in 40 mechanically ventilated patients with COVID-19 who underwent CT angiography 4–8 days after ICU admission [10]. Standard prophylaxis had been used in 22 patients, of whom 11 (50%) were diagnosed with PE. In contrast, PE was documented in only 2 of 18 (11%) patients who had received higher intensity prophylaxis. The authors concluded that higher intensity prophylaxis should be considered for critically ill COVID-19 patients admitted to the ICU [11]. While our study lacks an adequate comparison group of patients who received standard dose prophylaxis, we report a similarly low incidence of

| Table 1 |

| Clinical Characteristics of patients who experienced a thromboembolic event. |
|---------------------------------|
| Patients with thromboembolic events (n = 6) |
| Demographics | |
| Age (years) | 66 (45–71) |
| Male, n (%) | 5 (83.3) |
| BMI (kg/m2) | 24.7 (23.2–37.2) |
| D-Dimer (ng/mL) | |
| At admission | 8775 (687–43682) |
| Peak value | 6971 (687–43890) |
| Type of Event | |
| DVT | 4 |
| PE | 1 |
| Arterial embolism | 1 |
| Days from admission until event | |
| VTE prophylaxis regimen | |
| Low | 2 |
| Moderate | 3 |
| High | 1 |
| Outcome, n (%) | |
| Survived | 3 (50) |
| Decreased | 3 (50) |
thromboembolic disease amongst critically ill patients with COVID-19 who are treated with enhanced dose prophylaxis. Given the low rate of thromboembolic events and lack of bleeding, our experience would suggest that enhanced prophylaxis may be a safe and effective method of managing critically ill patients with COVID-19. In addition, recent preliminary data suggests that therapeutic dosing of anticoagulation for prophylaxis of critically ill patients with COVID-19 does not offer benefit and may be associated with harm [12].

Our study has several limitations. To our knowledge this is the largest study of an enhanced prophylaxis regimen in COVID-19 published to date, but it is nonetheless a retrospective analysis of the experience in a single ICU. A multicenter, prospective study comparing enhanced prophylaxis with alternative approaches to anticoagulation would better define the role of enhanced prophylaxis in critically ill patients with COVID-19. In addition, we diagnosed DVT and PE only when clinical suspicion led to appropriate imaging studies. Although screening studies to detect DVT or PE are not generally recommended [8], such an approach may have yielded a greater incidence of thromboembolic disease than we observed. Finally, since microvascular thrombosis that would not be readily identified by imaging modalities could potentially contribute to adverse outcomes in COVID-19, the benefit of enhanced prophylaxis would ideally be assessed not only by the rate of diagnosed thromboembolic event, but also by its impact on mortality.

In conclusion, in patients with COVID-19 admitted to the ICU, an enhanced thromboprophylaxis strategy appears to be effective at preventing clinically significant thromboembolic events with a low risk of significant bleeding.

Fig. 1. Thrombotic and bleeding events at different levels of anticoagulation intensity.

![Thrombotic and bleeding events at different levels of anticoagulation intensity.](image-url)

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### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at [https://doi.org/10.1016/j.tru.2021.100048](https://doi.org/10.1016/j.tru.2021.100048).

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