

Review Article

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Prophylaxis and treatment of pulmonary thromboembolism in COVID-19 patientsReza Shojaee¹; Saeed Karimi Matloub²; Rasool Karimi Matloub^{3*}¹Vascular Surgeon, Department of Surgery, Arak medical university, Iran.²Qom University of Medical Sciences, Iran.³Arak University of Medical Sciences, Iran.***Corresponding Author: Rasool Karimi Matlou**

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Keywords: coronavirus; COVID-19; pulmonary thromboembolism.**Abstract**

In 2019, a completely unique pneumonia, called coronavirus disease 2019 (COVID-19), spread rapidly throughout the planet. This novel global pandemic severely threatened public respiratory health and medical services. To date, apart from the common respiratory symptoms, coagulation disorders, especially Pulmonary Thromboembolism (PTE), has been proven as a crucial complication in severe COVID-19 patients, and therefore the incidence of PTE causes poor clinical outcome and increased fatality. Therefore, it's important that healthcare providers, including respiratory physicians, medicine specialists, hematologists, cardiologists, communicable disease specialists, and other specialists, recognize that patients with COVID-19 are at increased risk of PTE, and make sure that appropriate prophylaxis is run to the acceptable patients, which they effectively manage PTE when it does occur. The mechanism of PTE in patients with coronavirus pneumonia consists of endothelial injury, activated platelet, cytokine storm, and a suppressed fibrinolytic system. Early prophylaxis, antiviral therapy, anticoagulation, and supportive treatment are beneficial to COVID-19 patients. In this review, we summarize the harm that coronavirus pneumonia wreaks and highlight the clinical relationship between PTE and coronavirus infection. The potential mechanism and therefore the prophylaxis and therapeutic measures also are discussed to involve more effort and research to research the strategies for PTE in COVID-19.

Introduction

Several reports have described significant procoagulant events, including life-threatening Pulmonary Embolism (PE), in covid-19 patients. The incidence of PE is reported to be around 2.6–8.9% of COVID-19 in hospitalized patients and up to one-third of these requiring medical Care Unit (ICU) admission, despite standard prophylactic anticoagulation. This may be explained by direct and indirect pathologic consequences of COVID-19, complement activation, cytokine release, endothelial dysfunction, and interactions between differing types of blood cells [1-45].

Evidence of PE may found in patients who underwent CTA imaging. Interestingly, comorbid conditions were similar in patients with PE and people without [29,30]. The incidence of PE in hospitalized patients with COVID-19 has been reported to be around 1.9-8.9% [29,33,43,44].

Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is associated with coagulation abnormalities which predispose to considerable procoagulant effects [56-60].

The onset of PTE varied from 2-4 weeks after the occurrence of the initial symptoms of SARS-CoV-2 infection and led to deterioration of the clinical picture altogether cases. In 100 hospitalized patients with COVID-19, Grillet et al. found radiologic evidence of PTE in 23% of cases in CTA, performed within the typical of 12 days after the onset of symptoms [61]. Coagulation activation has been reported in COVID-19, determining pathological changes specifically involving the lung microvasculature, and an increased risk of DVT, PE, and DIC in severe phase. The use of anticoagulants, especially heparin, is suggested by expert consensus for patients with severe COVID-19, although a final guidance can't be implemented yet. There are several ways in which probably heparin administration can benefit patients with COVID-19, beyond the anticoagulant effect [65].

Discussion

PTE is defined as a thrombus that blocks the circulation and it can cause acute rises of pulmonary vascular resistance and therefore the afterload of the proper ventricle which will finally induce right coronary failure and shock. PTE and deep phlebothrombosis (DVT) are collectively mentioned as venous thromboembolisms (VTEs) and that they are considered because the different clinical manifestation of VTEs in several time and at different locations [66].

PTE may be a potential life-threatening complication, which occurs frequently in patients with COVID-19. Intermediate therapeutic dose of anticoagulants are often considered in patients with COVID-19 with risk factors for VTE, especially those requiring ICU admission. Extending thromboprophylaxis after hospital discharge or during home self-isolation may be reasonable after meticulous risk/benefit assessment, especially in patients with high risk of VTE [62].

The ISTH and therefore the American Society of Hematology (ASH) [46-49] have recently recommended that a prophylactic dose of LMWH (40 mg qd) [50] or subcutaneous unfractionated heparin (5000 IU tid)-should be started altogether suspected or confirmed COVID-19 patients admitted to the hospital. In patients with known heparin-induced thrombocytopenia, fondaparinux [50,51], which was found to be effective in reducing sepsis-derived coagulopathy in an animal model [52], should be used. If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis (e.g., intermittent pneumatic compression) should be considered in immobilized patients [46]; combined pharmacologic and mechanical prophylaxis is not generally recommended [51]. Although limited data are available, it's reasonable to think about pharmacological thromboprophylaxis in patients admitted to hospital with COVID-19 infection, even in pregnant women, since they're likely to be at an increased risk of VTE [46]. The use of and intermediate dose of LMWH (e.g., enoxaparin 4000 IU subcutaneously every 12 h) are often considered on a private basis in patients with multiple risk factors for VTE [53] and in critically ill patients thanks to the upper incidence of PE during this population [29-41]. In obese patients, higher weight-based doses could also be needed, with doses of 7500 IU UFH 3 times daily or enoxaparin 40 mg twice daily [54,55]. While the sort of therapeutic anticoagulant wasn't described in 4 included studies, heparin-based anticoagulants (UFH and

LMWH) were the foremost frequent sort of anticoagulants reported within the other studies. These findings may reflect current supposition among physicians that heparin may have therapeutic effect in COVID-19 beyond its anticoagulant properties. Heparin is postulated to wield both antiviral and anti-inflammatory effects through inhibition of viral entry and dampening of pro-inflammatory signals, respectively [63]. Even though these theoretical hypotheses are biologically plausible, it still lacks strong evidence in supporting these effects. Furthermore, whether heparin-based anticoagulants are superior to DOAC or VKA in terms of clinical outcome in patients with COVID-19 requires further study [64]. A meta-analysis by Lippi et al. revealed that thrombocytopenia was a standard feature in critically ill COVID-19 patients [weighted mean difference $-31 \times 10^9 /L$; 95% confidence interval (CI), from -35 to $-29 \times 10^9 /L$] and the decrease of platelet count was associated with the increased risk of severe disease and deaths in COVID-19 patients [67]. In contrast, some studies have reported that no significant difference of platelet count existed between the severe COVID-19 patients and moderate patients [68-70]. Lastly, a study also showed that the platelet count in COVID-19 patients with DVT wasn't significantly different from those without DVT [71]. Moreover, Qu et al. found platelet peaks and Platelet-to-Lymphocyte (PLR) at the platelet peak were associated with the severity and duration of COVID-19 patients [72]. However, some cases reported an elevated platelet count in severe COVID-19 patients and this phenomenon was considered because the over-activation of platelets resulting from the over-production of proinflammatory factors and the formation of a cytokine storm [72,73]. Therefore, the platelet count can vary with each individual and therefore the specific relation between platelets and COVID-19 needs more research to reveal it.

Anticoagulant treatment is significant for all patients with PTE, which may effectively prevent the thrombosis from forming and relapsing and activating the human fibrinolytic system. Tang et al. reported that the utilization of heparin, mainly LMWH, achieved good clinical outcomes and notably decreased the 28-day mortality in severe COVID-19 patients with coagulation disorders compared with those not receiving heparin treatment (40.0% versus 64.2%, $p = 0.029$) [74]. Moreover, heparin can inhibit the inflammatory response in body and protect the endothelium of the microvessels [75], which suggests that heparin plays an important role in treating COVID-19 patients with PTE in various ways. However, the concrete dose of heparin should be carefully administered by clinical doctors on the idea of specific conditions and therefore the risks of anticoagulation treatment, especially the threat of uncontrolled massive hemorrhage, should be weighed and considered in detail [66].

Conclusion

Patients with COVID-19 are at increased risk of developing PE which can occur in up to one-third of critically ill COVID-19 patients requiring ICU admission. Thromboprophylaxis should therefore be started in COVID-19 patients admitted to the hospital and intermediate therapeutic doses of anticoagulants are often considered in patients requiring ICU ad-

mission or those with multiple risk factors for VTE. Extending thromboprophylaxis after hospital discharge or within the prehospital phase during home self isolation should be done consistent with a meticulous risk/benefit assessment, balancing the reduced risk of VTE with the risk of increased bleeding events. Therapeutic anticoagulation is that the cornerstone within the management of patients with PE. Selection of an appropriate agent and proper dosage requires consideration of underlying comorbidities and organ dysfunction. Based on the findings, it seems that thromboembolic events should be considered as a possible explanation for clinical deterioration in COVID-19 cases and in-charge physicians should consider PTE as a medical diagnosis for worsening of dyspnea in these cases. In conclusion, the infection of CoVs, especially SARS-CoV-2, can frequently induce coagulation disorders and PTE, which can cause the deterioration of the patient, organ failure, and mortality in those with coronavirus pneumonia. The mechanism of PTE in coronavirus pneumonia patients, including pulmonary thromboembolism and therefore the formation of primary thrombosis in pulmonary vessels, contains four aspects: The damage of the pulmonary vessel endothelium, the assembly of excessive proinflammatory factors and a cytokine storm, the aggregation and adhesion of platelets, and therefore the suppression of the human fibrinolytic system. Advanced assessment and prophylaxis, including both pharmacological and mechanical prophylaxis, could even be beneficial to decrease the occurrence of PTE. For coronavirus pneumonia patients with PTE, antiviral treatment, anticoagulation treatment, and symptomatic and supportive treatment can effectively promote the clinical outcome and reduce the death rate. To date, the interdisciplinary communication and integration among academia, industry, government organizations and clinical medicine are applied within the outbreak of COVID-19 to know the suitable methods for diagnosis and therapeutics. With the assistance of multidisciplinary cooperation and research, scientists can find better strategies for diagnosis, prophylaxis, and therapy for PTE in patients with coronavirus pneumonia.

Declarations

Conflicts of interest: The authors declare no conflict of interest.

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