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Use of Low Molecular Weight Heparin in Covid-19 Patients

Aishwarya Anand[1]*, Radhika. A. R[1]

[1]Department of Doctoral Student at Hasso Plattner Institute of Potsdam, Brandenburg, India

***Correspondence to:** Aishwarya Anand, Department of Doctoral Student at Hasso Plattner Institute of Po tsdam, Brandenburg, In dia, E-mail: aishwaryaaaanand1@gmail.com

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Abstract

A number of organ-specific and systemic phenotypes have been added by the COVID-19 pandemic, others previously identified in viral infections, including severe acute respiratory syndrome (SARS) and others that seem to be unique to SARS-coronavirus (CoV)-2. The Coronavirus disease 2019 (COVID-19) pathogenesis is increasingly being recognized. Along with the mortality benefits of Heparin, a high number of thrombotic episodes are recorded. It is possible to view COVID-19 as a prothrombotic illness. Management recommendations are driven by increasingly evolving information from scientific observations, autopsy-based results, and extrapolations from in vitro and ex vivo experiments and complex modelling; however, several issues remain unanswered and scientific trials that are needed to include proof in most fields have not been conducted. Also, this is supported by several coagulation markers. COVID-19 can be considered as a thrombosis risk factor. Objective: The following review summarizes emerging findings into pathobiology, mechanism(s), diagnosis, administration, scientific foundations, and proposed or continuing COVID-19-associated coagulopathy clinical trials and use of Heparin in COVID-19 patients. Conclusion: Stratifying high-risk thrombosis patients, particularly the elderly, those with comorbidities and high D-Dimer levels is an important step to prevent thromboembolism in COVID-19 patients.

Keyword: COVID-19; thrombosis risk factor; use of Heparin

Introduction

In Wuhan, Hubei province, China, several cases of pneumonia of unknown etiology were registered at the beginning of December 2019. The World Health Organization announced in January 2020 that a new form of coronavirus (SARS-CoV-2) was responsible for this. The distribution of SARS-CoV-2 has been exponential, with more than two million confirmed cases resulting in a worldwide pandemic. Although most COVID-19 individuals experience only mild disease, marked by fever and continuing cough, about 14% experience serious disease requiring hospitalization and oxygen treatment, and 5% require intensive care admission. COVID-19 patients with respiratory depression mainly have extreme hypoxemia, but compliance with the respiratory system will range from near average to extremely low. COVID-19 patients experience a form of acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure in serious cases. Greater mortality is associated with older age and co-morbidities. The virus has a very high capacity for transmission which, in the absence of barrier steps which stringent means of control, can spread easily in an accelerated fashion that contaminates thousands of people. There is no country spared. The virus causes acute respiratory failure caused by cellular lesions in the lungs with a rapid evolution that involves mechanical ventilation and a mortality rate varying from 1 to 10%.

A rise in thromboembolic problems in COVID 19 has been observed. This are manifested by pulmonary embolisms or systemic microembolisms that damage the lungs, brain, liver, kidneys and intestines by microangiopathy. It can also affect the retina. By activating it and inducing lesions, the virus has the potential to cause the endothelium pro clot. During the second week of the disease cycle, these thromboembolic symptoms are commonly found. The magnitude of the pathology is due to the immune response of the host and not to the overt intervention of the virus. The magnitude of the symptoms is related proportionally to the rise in the number of antibodies. Indeed, these virus neutralization antibodies cause a secondary plasma protein S deficiency or malfunction that is responsible for thromboembolic events. An significant therapeutic agent in extreme types of the condition is activated protein C, a biochemical regulator of coagulation.

The SARS-CoV-2 coronavirus outbreak, called COVID-19, has been a worldwide emergency. The virus spreads through respiratory droplets and is mainly responsible for respiratory airway infections and potentially fatal pneumonia.While mortality in elderly vulnerable patients with comorbidities is higher, cases of death have been recorded in younger age groups as well. The SARS-CoV-2 virus, a member of the Coronaviridae family that comprises the SARS-CoV (Severe Acute Respiratory Syndrome-Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome-Coronavirus) viruses responsible for outbreaks of serious respiratory diseases, is caused by COVID-19. It is recognized originally as an acute respiratory distress syndrome (ARDS). It was soon realized that the involvement of the heart, brain, and kidney in COVID-19 was also common. Interestingly, there were records of a higher than normal number of thrombotic cases in patients with COVID-19. Advanced age and comorbidity are predictors of elevated COVID-19 mortality that could be linked with thrombosis

vulnerability in these persons.Novel and unforeseen problems are being faced by the doctors treating patients with COVID-19. Most of them is the proper treatment and management of venous thromboembolism (VTE) and, more commonly, how to cope with coagulative activation clearly present in these patients. While several viruses are associated with haemorrhagic fever, few viruses are known to cause thrombosis.Initial autopsies of patients with COVID-19 had microthrombi in the lung vasculature. In a subgroup of patients, the observation of Heparin providing a survival advantage attracted attention to the thrombosis prevalent in COVID-19. Lung compliance during mechanical ventilation is not decreased in the early stages of the illness. In 16 patients, lung compliance was studied and considered atypical for ARDS.Therefore, maybe the hypoxia could be more due to other variables than ARDS at the initial level. This can be explained by the depletion of haemoglobin's oxygen delivery potential and reduced gas exchange in alveoli with microthrombi. Altered lung perfusion and hypoxic vasoconstriction can be caused by the microthrombi, worsening hypoxemia.In COVID-19, venous thromboembolism is prevalent. In 15% of COVID-19 patients with pneumonia and elevated D-dimer, deep vein thrombosis was observed by Doppler ultrasound. Diabetes patients who develop COVID-19 tend to be at greater risk for thrombosis. The appearance of chilblain-like lesions in the periphery of COVID-19 patients that may be clarified by vasculopathy is other support for the function of thrombosis. In addition, an atypical Kawasaki-like syndrome identified in COVID-19 may display medium vessel vasculopathy again. We plan to review thrombosis as an important part of COVID-19 in this article and address the many recent questions regarding the use of Heparins and the proper prevention and diagnosis of VTE in patients with COVID-19.

COVID-19 as a Risk Factor of Thromboembolism and VTE

In a very limited number of COVID-19 cases, autopsies have been conducted. In arterioles and venules, several of these experiments show venous thromboembolism and microthrombi. There are several cases of both arterial (stroke, myocardial infarction) and venous thrombosis (deep vein thrombosis, pulmonary thromboembolism, venous sinus thrombosis) in COVID-19 patients. Many of these patients have conventional risk factors for thrombosis. Obesity and poorly regulated diabetes mellitus, state which can exacerbate hormonal processes such as breastfeeding and contributers to venous and arterial thrombosis, are the most important risk factors in the sense of COVID-19.

Acute infections are associated with a temporary elevated risk of VTE and the prototypical example of acutely ill care patients at increased risk of VTE is the subjects treated with COVID-19 pneumonia. Indeed, not only do admitted COVID-19 patients suffer from an acute infection, they also suffer from respiratory failure and are bedridden or have decreased movement due to the need for supplementation of oxygen and the loneliness caused by hospital constraints. Interestingly, pregnancy may also raise the risk of placental thrombosis in women infected with the coronavirus. Fetal vascular malperfusion or foetal vascular thrombosis was documented in a case series of 20 pregnant women with COVID-19 primarily due to intravascular fibrin deposition, although the clinical relevance of this placental phenomenon remained unclear.

Very little is currently known about the precise occurrence of VTE in hospitalized COVID-19 pneumonia patients. This is due to the fact that medical tests of these patients are not easy to do, since they must stay of isolation, there is a chance of virus aerosolization, there is also a shortage of adequate personal protective equipment, or patients are too unstable. The implication is that there are only two reports conducted on this topic right now, both carried out on patients aided in Intensive Care Units (ICUs). In the Netherlands, the first study reported a remarkable 27% incidence of VTE (including both DVT and PE), confirmed by either computed tomography pulmonary angiography (CTPA) and/or venous leg ultrasound, out of a total of 184 patients evaluated. The second study was performed in China and recorded a 25 percent prevalence of DVT, measured by venous leg ultrasound, in a total of 81 patients examined. It is very important to find out that all patients received at least standard doses of anticoagulant thromboprophylaxis in the Dutch study, while no preventive anticoagulant was given to patients in the Chinese study. There are two 'preprints' in addition to these studies, which are early papers that have not received peer review, and case papers. Four cases of deep vein thrombosis (DVT) among 138 COVID-19 patients consecutively admitted to hospital in China are recorded in one of these preprints, with a prevalence of 2.9%. The authors of this study point out that three of these DVTs have been detected in critically ill patients, suggesting that the incidence of VTE may be higher in subjects with severe COVID-19. Another preprint reports that 25 of 1008 COVID-19 pneumonia patients underwent CTPA and 10 were found to have PE. Taken together, these results support the hypothesis that the clinical course of COVID-19 pneumonia might be complicated by VTE. It is also well known that acute PE in viral pneumonia is a source of clinical decline.

Not to mention the fact that, as in the case of the 75-year-old woman mentioned by Danzi and coll, several COVID-19 patients remain at home with fever and respiratory symptoms for several days before being admitted, and therefore could already have VTE at the time of hospital admission. For these factors, some hospitals are considering routine screening of deep vein thrombosis (DVT) using leg ultrasonography among all COVID-19-positive hospitalized patients.

Heparin Use in Severe COVID Infection

A retrospective study performed at Tongji Hospital in Wuhan, China, recorded that only 99 (2%) of the 449 patients with extreme COVID-19 had received Heparin (mainly Low Molecular Weight Heparin, LMWH) medication for 7 days or longer. The 28-day mortality rate for participants with a Sepsis-Induced-Coagulopathy (Sic.) score of 4 was higher for Non-Heparin than for Heparin treated patients. The authors of this retrospective study rightly point out that in this population, anticoagulation was rarely used because there was a poor knowledge of the disease at the time of its hospitalization, and they state that

Heparin was gradually used later during the outbreak of COVID-19 in China. The International Society on Thrombosis and Haemostasis (ISTH) now advises the use of prophylactic doses of LMWH for all admitted patients with COVID-19, unless they have active bleeding or platelet counts < 25 × 109/L. The mortality benefit of Heparin after age and gender change was also confirmed by a broader observational analysis of evidence from 17 Spanish hospitals.

Heparin also has antiarrhythmic properties beyond the gain of anticoagulation and can also oppose traditional RAAS activation. The International Society of Thrombosis and Hemostasis (ISTH) has indicated that, even in the absence of other characteristics, patients with elevated D-Dimers should be admitted because this indicates increased production of thrombin. For all hospitalized patients, including non-critically ill patients, Low-Molecular-Weight-Heparin (LMWH) has also been prescribed. Similarly, the American Society of Hematology (ASH) states that all COVID-19 hospitalized patients should receive LMWH or Fondaparinux pharmacologic thromboprophylaxis unless they are considered to be at increased risk of bleeding. However, the medical community has a clear feeling that prophylactic doses of anticoagulation might not be appropriate to compare the hypercoagulable condition demonstrated by many patients with COVID-19 in addition to cytokine storm syndrome. In this case, some clinicians, based on the anti-inflammatory effect of Heparin and also its anti-viral capacity, are considering a higher dose of anticoagulation in patients who do not have reported VTE. It should be recalled, in any event, that the use of anticoagulation at doses other than those typically used for thromboprophylaxis is currently not confirmed by any reported data, but rather by realistic considerations. In fact, the true occurrence of VTE remains unknown in COVID-19 patients undergoing pharmacological thromboprophylaxis, as discussed here, and there is a lack of evidence suggesting better results in patients treated with therapeutic anticoagulation. Physicians around the world make decisions on a case by case basis in this puzzling situation, and therapy regimens are very heterogeneous from hospital to hospital, even within the same country.

Conclusion

Infections with COVID-19 are distinguished by highly varied phenotypic expressions affecting most main organs and structures of organs. An acquired condition known as coagulopathy associated with COVID-19 has arisen and has shown itself to be widespread, multifactorial with venous, arterial and microcirculatory systems involvement and distinct from other viral diseases. The existing data points to a risk for COVID-19 thrombosis. Bleeding is uncommon except though thrombocytopenia happens. The evidence available distinguishes COVID-19-associated coagulopathy from DIC and early-stage thrombotic microangiopathy, and while anticoagulant treatment for thromboprophylaxis has been prescribed by all major societies in the fields of cardiology, haematology and thrombosis, optimal treatment has not yet been identified through comprehensive clinical trials. Despite the prophylactic and medicinal use of Heparin, thrombosis can occur. There is an immediate need to stratify high-risk thrombosis patients, particularly the elderly, those with comorbidities and high D-Dimer levels.

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