



Thrombosis in COVID-19 Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The magnitude of thrombosis in Coronavirus disease 2019 (COVID-19) patients is yet to be understood fully. Thrombosis in COVID-19 patients depends on multiple factors like the severity of the disease, presence or absence of prophylactic anticoagulants, and the number of anticoagulants prescribed. Histologically, lung tissues from COVID patients show florid capillary endothelitis with microthrombi formation in alveolar capillaries and small pulmonary vessels. Inflammation and diffuse alveolar damage, extensive pulmonary macrophage activation and diffuse interstitial inflammation play an important role in microthrombi formation in the pulmonary vessels. If antithrombotic therapy is already prescribed before the diagnosis of COVID-19, it should be continued. For all hospitalized pregnant patients, prophylactic anticoagulant therapy is prescribed unless contraindicated. Anticoagulant therapy during labor requires special care. Appropriate therapeutic and prophylactic anticoagulant regimens must be initiated as and when required including in the post discharge phase.

Keywords: Florid capillary endothelitis; COVID-19; anticoagulant regimens; anticoagulant therapy.

1. INTRODUCTION

At the end of 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) has resulted in acute respiratory illness epidemic which was termed as COVID-19 by the World Health Organization (WHO) [1]. Coronavirus disease 2019 (COVID-19) was

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declared as a pandemic in March 2020 and has been affecting the world.

Covid-19 may predispose to both arterial and venous thromboembolism due to excessive inflammation, hypoxia, diffuse intravascular coagulation and immobilization [2]. Knowledge on thrombotic complications in COVID-19 is a must to provide proper thromboprophylaxis to patients especially those admitted in intensive care unit (ICU) to control the risk of such complications.

Pulmonary embolism and deep vein thrombosis are manifestations of venous thromboembolism [3]. They share common risk factors, and pulmonary embolism is a consequence of deep vein thrombosis.

The magnitude of thrombosis in COVID patients is yet to be understood fully. Thrombosis in COVID depends on multiple factors like the severity of the disease, presence or absence of prophylactic anticoagulants, and the number of anticoagulants prescribed. Along with affecting organs like lung and GI Tract COVID also leads to a hypercoagulable state.

2. PATHOPHYSIOLOGY OF THROMBOSIS IN COVID-19 PATIENTS

COVID-19 is a hypercoagulable state which is a sequel of hyper inflammation leading to increased mortality in these patients. Uncontrolled activation of coagulation cascade resulting from effects of pro inflammatory cytokines can lead to consumptive coagulopathy. Derangement of coagulation also includes disseminated intravascular coagulation (DIC) and sepsis-induced coagulopathy.

The coronavirus family enters the human cell by binding ACE 2(Angiotensin- converting enzyme 2), that is found mainly on alveolar endothelium and epithelium [4]. It has been postulated that COVID generates pro-inflammatory cytokines and chemokines in nearby endothelium, epithelium and alveolar macrophages. These proteins in turn attract inflammatory cells to the infection site causing a pro-inflammatory feedback loop. Tissue factor in sub endothelium is upregulated in the endothelial cells, leucocytes and platelets during inflammatory process causing both intrinsic and extrinsic coagulation pathway activation which leads to thrombin formation. Complement activation also occurs by binding thrombin to protease activated receptors

to promote the formation of fibrin from fibrinogen [5]. The activation of platelets and clot stabilization propagate further inflammation. Natural anticoagulants and fibrinolytics are also reduced in covid-19 infection. Small pulmonary vessels can get occluded and they may contain platelets, fibrin and coagulation factors. They may also contain neutrophils which gets into the neutrophil extracellular traps as they get passed through the lung. These and the ongoing inflammation can cause positive feedback loop. Some of the other procoagulant stimuli include lung hypoxia, maybe through upregulation of plasminogen activator inhibitor 1 by suppression of fibrinolysis [5]. Prothrombotic pneumonitis and acute respiratory distress syndrome is thought to be induced by the above mechanism. Inflammatory process can influence D-dimer levels [6]. D-dimer is a product of degeneration of fibrin and acts as a marker for fibrinolysis which can be used as an indicator of thrombosis. It is elevated in thrombotic events [7].

Histologically, lung tissues from COVID patients show florid capillary endothelitis with microthrombi formation in alveolar capillaries and small pulmonary vessels. Inflammation and diffuse alveolar damage, extensive pulmonary macrophage activation and diffuse interstitial inflammation play an important role in microthrombi formation in the pulmonary vessels [6].

3. INCIDENCE OF THROMBOSIS IN COVID-19 PATIENTS

A number of studies have reported a high incidence of thrombotic and thromboembolic events in COVID-19, especially in patients with severe disease admitted in ICU. Klok et al.⁸ identified thrombosis in 31% of 184 Dutch ICU patients (25 Pulmonary Embolism, 3 Deep Vein Thrombosis and 3 ischaemic strokes) [8]. They observed that increasing age and coagulopathy were independent predictors of outcome. All patients in this study had received thromboprophylaxis. (a minority at doses higher than the usual prophylactic dose). Helms et al.⁹ demonstrated Pulmonary Embolism in 17% of 150 COVID-19 ICU patients (25% patients underwent CT Pulmonary Angiogram; 70% patients were receiving prophylactic heparin and 30% therapeutic dose heparin on intensive care admission)[9]. Middeldorp et al.¹⁰ demonstrated that the incidence of venous thromboembolism was higher in COVID 19 patients admitted to Intensive Care Unit (26%, 47% and 59% at 7, 14

and 21 days respectively). According to this study 13% had symptomatic thromboembolism in spite of routine thrombo-prophylaxis, Venous thromboembolism was observed more in ICU patients [10]. Tang et al.[11] showed that the overall mortality among COVID patients admitted to hospital was 11.5%, and that non-survivors had significantly higher D-dimer and fibrin degradation product levels, longer prothrombin time and activated partial thromboplastin time compared to survivors on admission. This study also revealed that 71.4% of non-survivors and 0.6% survivors met the criteria of disseminated intravascular coagulation during their stay at the hospital [11]. There is another type of thrombosis observed in COVID-19 patients, cerebral venous thrombus (CVT). The incidence of CVT is low and the available data is limited. Hameed et al. [12] showed that the common presenting symptom of CVT is seizures and headache, 65% presented with cerebral venous thrombus on admission while 35% developed CVT during treatment for COVID [12]. Elezkurtaj et al. [13] demonstrated that 23.1% of COVID patients died due to pulmonary thromboembolism and 7.7% of COVID patients died from deep venous thromboembolism and the rest died due to other complications [13].

4. DIAGNOSIS OF THROMBOSIS IN COVID-19 PATIENTS

Thrombosis is diagnosed by clinical suspicion, laboratory data and imaging. Diagnosis of thrombosis is challenging in COVID-19 patients due to many reasons such as overlapping symptoms of respiratory failure and hypoxia, technical difficulties in obtaining data from hemodynamically unstable critically ill patients on life saving support systems, initiation of treatment before confirming diagnosis due to rapid deterioration of patient and infection precaution measures. COVID-19 patients are predisposed to many complications such as hepatic, renal and respiratory complications, which often pose a challenge in the timely diagnosis and management of thrombotic events. But prompt evaluation of these thrombotic events is crucial for the treatment of these patients.

A high index of Clinical suspicion is key in the diagnosis of thrombotic events in such a complex scenario. The patient may exhibit symptoms such as tachypnea, decreased oxygen saturation, increased oxygen requirement and hemodynamic instability which may be inconsistent with features of imaging studies.

Edema or asymmetrical limb pain can indicate deep vein thrombosis(DVT)[14]. Even if imaging or definitive diagnosis is not available, anticoagulant therapy should be started if clinical features supporting thrombotic events are present.

Laboratory parameters are important for the diagnosis of thrombotic events. Any derangements in the coagulation parameters cause the activation of coagulation cascade. Findings indirectly indicate increased risk of thrombosis, disease severity and mortality. Raised von Willebrand factor can indicate endotheliopathy. Studies have shown that in COVID-19 patients D-dimer, fibrin degradation products, fibrinogen degradation products and fibrinogen are found to be increased [15]. It has also been found that D-dimer levels, C-reactive protein and fibrinogen degradation products were higher in patients with severe COVID-19 infection when compared to mild infection [5]. Antiphospholipid antibodies may also have an important role in identification of thrombotic events but there is a greater chance of false positive reports.

Imaging studies help to find a definitive diagnosis of thrombosis. Ultrasound and computer tomography pulmonary angiogram (CTPA) are useful for identification of deep venous thrombosis or pulmonary embolism. Point of care ultrasound is an effective method to identify thrombosis especially in critically ill settings. Ultrasound is more useful in pregnant women as it prevents them from exposure to radiation. Early detection is important and imaging findings must be correlated with clinical features. They are used to diagnose thromboembolism in patients in need of extracorporeal membrane oxygenation (ECMO), renal replacement therapy (RRT) and in patients with prior anticoagulant requirement like patients with atrial fibrillation, mechanical valves or recurrent venous thromboembolism[5].

5. DRUGS TO TREAT/PREVENT THROMBOSIS IN COVID-19

Anticoagulants are used for the treatment and prevention of thrombosis. Based on their action, anticoagulants are divided into different categories.

Heparin is a true anticoagulant which includes unfractionated heparin (UFH) and low molecular weight heparin (LMWH). It acts by forming

activated factor X and protease-heparin-antithrombin[5]. Heparin is used in the treatment of deep vein thrombosis and pulmonary embolism, especially in patients undergoing dialysis, cardiovascular and orthopedic surgeries, extracorporeal circulation and other invasive procedures. Heparin is not only used for its anticoagulant effect but also for its anti-inflammatory effect in patients with COVID-19. Heparin also has protective effects on the endothelium. Unfractionated heparin has antiviral effects for coronavirus infection. Some of the disadvantages of heparin are bleeding, hyperkalemia, alopecia and injection site reaction.

Warfarin, a vitamin K antagonist and other coumarin derivatives are also effective anticoagulants. Warfarin is a competitive inhibitor of VKORC1, causing decreased hepatic synthesis of vitamin-K dependent clotting factors including protein S and protein C. Warfarin therapy needs to be monitored closely due to a narrow therapeutic index and wide dosing range which are needed for maintaining therapeutic INR(international normalized ratio) and also because of numerous drug interactions[14].

Direct oral anticoagulants include both direct thrombin inhibitors and direct factor Xa inhibitors. These have higher safety profile, greater efficacy and requires less monitoring. Direct thrombin inhibitors include drugs such as Dabigatran and direct factor Xa inhibitors include drugs such as Apixaban, Edoxaban and Rivaroxaban. Some of the adverse effects of direct thrombin inhibitors are bleeding, liver injury and gastrointestinal disorders. Newer anticoagulants such as idarucizumab are used for clinical use but they are not globally available.

Indirect inhibitor of factor X asuch as Fondaparinux achieves anticoagulation by binding and activating antithrombin.

6. PROPHYLACTIC ANTICOAGULANT IN COVID-19 PATIENTS

6.1 Prophylaxis in Acutely Ill Patients (non-ICU)

The International Society on Thrombosis and Hemostasis has recommended the use of antithrombotic prophylaxis with low molecular weight heparin for all patients who are admitted unless there is a contraindication [16]. Fondaparinux is recommended if the patient has heparin induced thrombocytopenia [17]. Routine thromboprophylaxis is not recommended in

mobile patients with acute medical illness or respiratory symptoms. The choice of heparin is based on the individual patients depending upon factors like underlying renal dysfunction[16]. According to American Society of Hematology (ASH), prophylactic-intensity anticoagulant is preferred over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19 acute illness who do not have suspected or confirmed VTE[18]. Dose adjustment for obesity can be used as per institutional guidance. When anticoagulants are contraindicated, mechanical prophylaxis should be used [18].

6.2 Prophylaxis in Critically Ill Patients (ICU)

According to The International Society on Thrombosis and Hemostasis routine thromboprophylaxis with standard-dose UFH or LMWH should be used in all patients. Intermediate dose LMWH can also be used. Patients with obesity should be considered for 50% increase in dose [16]. COVID-19 patients who are critically ill may develop liver dysfunction which results in worsening of coagulopathy. These patients are at increased risk of bleeding. Individualizing the dose of anticoagulants based on their clinical picture is important to prevent adverse bleeding incidents [5].

6.3 Post-Discharge Prophylaxis

Patients admitted to the hospital for acute illness have an increased risk of developing thrombotic events up to 90 days after discharge. So same risk is to be expected in patients with COVID-19 infection. Hence extended anticoagulant treatment after discharge is given to patients, especially those who are discharged from critical care units. Risk of bleeding should also be considered while providing with anticoagulants post-discharge[5]. According to The International Society on Thrombosis and Hemostasis extended thromboprophylaxis should be considered in patients who meet the high thrombosis risk criteria. They recommend the duration of thromboprophylaxis to be at least 14 days and may continue up to 30 days[16].

7. THERAPEUTIC ANTICOAGULANT IN COVID-19 PATIENTS

Critically ill patients with COVID-19 demonstrated a more hyper fibrinolytic and hypercoagulable profile on comparison with patients with mild

COVID-19 illness. This hypercoagulable profile was observed despite the therapeutic anticoagulant doses[19], and in COVID-19 patients with severe illness, therapeutic anticoagulation did not improve hospital survival or days free of organ support when compared with usual care pharmacological thromboprophylaxis [20].

Therapeutic anticoagulant regimen should be started in patients with COVID-19 who have experienced an incident thromboembolic event or who have had suspicion of thrombotic events. Patients who are on continuous renal replacement therapy or have thrombosis of the catheters or require extracorporeal membrane oxygenation should be given therapeutic anticoagulant regimen. Low molecular weight heparin is given at a dose of 1mg per kilogram and in case the patient has renal failure or suspected of going into renal failure then UFH is used instead of low molecular weight heparin[21]. Measurement of anti-factor Xa level may be helpful to identify heparin resistance in these patients.

8. ANTICOAGULANT THERAPY IN PREGNANT/LACTATING MOTHERS

If antithrombotic therapy is already prescribed before the diagnosis of COVID-19, it should be continued. For all hospitalized pregnant patients, prophylactic anticoagulant therapy is prescribed unless contraindicated. Anticoagulant therapy during labor requires special care. Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in the breast milk and does not affect the baby so it can be used in breast feeding mother [22]. Direct-acting oral anticoagulants should not be used in pregnancy. Decision for administration of anticoagulants in postpartum or pregnant patients after discharge should be individualized based on their risk profile [22].

9. CONCLUSION

COVID-19 is an ongoing pandemic. We now recognize that thrombotic events are common in COVID-19 patients. It indicates that there is a multisystem involvement through inflammatory cytokines and the ensuing endothelial injury triggers the activation of the coagulation cascade leading to thromboembolic events [5]. Elevated D Dimer levels are almost universal in severe forms of disease and are an indication of inflammation and thrombosis. They are also prognostic.

Diagnosis of thrombotic events in COVID patients is challenging. D-dimer levels must not be the sole indicator for making decisions on diagnosis and treatment of thrombotic events in these patients. The clinical context is paramount and the physician must always maintain a high index of suspicion. This will enable early diagnosis of thrombotic events which is very important for effective treatment. Appropriate therapeutic and prophylactic anticoagulant regimens must be initiated as and when required including in the post discharge phase.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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