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Mini Review

COV-19 Vaccines-Induced Hypercoagulability and Its Therapeutic Management

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Abstract

A thrombotic complication is one of the severe clinical outcomes of COVID-19. Various pathophysiological mechanisms for thrombotic events in COVID-19 have been proposed. Consistently, elevated D-dimer level has emerged as an independent risk factor for poor outcomes, including death. Several other laboratory markers and blood counts have also been associated with poor prognosis, possibly due to their relation with thrombosis. At present, the pathophysiology underlying the hypercoagulable state is poorly understood. As a result, most critically diseased COVID-19 patients are managed with prophylactic anticoagulant. The management of COVID-19 was based generally on supportive therapy and treatment that prevent respiratory failure since it's directly effects on human respiratory system. However, antiviral now and other medications alongside vaccination are used. Vaccination also found to cause thrombosis symptoms are in many COVID-19 recipients. Vaccine-induced immune thrombotic thrombocytopenia was clearly recorded with significant and awful outcomes. No clear cause for this syndrome, but many hypotheses have been established to explain the mechanism of thrombosis formation. An interaction between platelets or platelet factor 4 with anti-PF4 is a similar point in the pathogenesis of problem. Since covid19 and its vaccine induce hyper-coagulability condition, it was found that anticoagulation therapy may block or slow progression of thrombosis formation. Treatment of COVID-19 vaccines-induced hypercoagulation include many intents; as anti-inflammatory, antithrombotic and antiviral drug. This can be done by one drug like low dose aspirin or more as warfarin that use as anticoagulant. Direct oral anticoagulant can also be used. Sometimes, combination of low dose aspirin and clopidogrel may be given as they are very effective. Focusing on treatment of thrombosis in COVID-19 has increased lately, consequently, many drugs like dipyridamole, (which is significantly improved platelet and lymphocytes count and decrease D-dimer level) become use for patient and more studies about its effect are done to reach a very effective treatment.

Keywords: Anticoagulant, Antiplatelet, COVID-19, Hypercoagulability, Thrombosis, Vaccine

Introduction

The novel coronavirus, SARS-CoV-2, belongs to the coronaviridae family, which are positive-sense single-stranded enveloped RNA viruses. It was initiated in WUHAN, is caused by sever acute respiratory syndrome coronavirus 2 (SARS-COV-2).[1] It was named as the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) by the international committee on Taxonomy of viruses (ICTV), since it is similar to previous SARS-COV.[2] The beginning of novel corona-virus was mentioned firstly by the World Health Organization (WHO) on December 31, 2019.[3] Since its outbreaks, covid-19 has spread rapidly around the world cause a huge effect on human life.[4] Population, economic growth and many of normal life manifestation was badly affected by this on-going pandemic.[5] It has caused a large mortality globally since December of 2019.[6] 20% of infected individual become severity ill and 2-5% die.[7] Respiratory failure is the most common cause of death, but excessive inflammatory reactions that lead to coagulation end by multiple organ failure are also cause of death.[8] Coagulation and other haematological disorders result from covid-19, related to increase D-dimer, fibrinogen, and factor VIII (EVIII) level was occurred.[9] In coronavirus disease 2019 (COVID-19), multiple thrombo-inflammatory events contribute to the coagulation

system activation, suppressed fibrinolysis, vascular endothelial cell injury, and prothrombotic alterations in immune cells such as macrophages and neutrophils.[10] Due to all of these, many potential was intensified for vaccine development against COVID-19, that was absolutely important for the prevention and control of this disease.[11] Currently, much managements are taken place to deal with COVID effects and how to treat them. This present review aims to highlight the current understanding of the pathophysiology and etiogenesis of COVID-19 related coagulopathy and hematological parameters either in vaccinated or non-vaccinated diagnosed cases. Additionally, the current review illustrates the rationale for use of anticoagulants, thrombolytic and antiplatelet drugs in different COV-19 therapeutic protocols.

Causes of Hyper-Coagulability During COV-19 Infection

Thrombotic complications are one of the severe clinical outcomes of COVID-19, especially among critically ill patients. The hypercoagulable state in COVID-19 is considered as emerging state as it associates with poor prognosis with a major pathological occurrence with serious consequences in mortality and morbidity. The pathophysiology of COVID-19 associated hypercoagulability is not fully understood. In comparison to venous thrombosis, the incidence of arterial thrombosis in COVID-19 appears to be minor. The Pulmonary embolism is the most common thrombotic manifestation of COVID-19.[12]

Various factors have been reported to be associated with increased risk for coagulopathies among COVID-19 patients. These include patients' age, and having of chronic disease such as cardiovascular disease, diabetes, and hypertension.[13] So COVID-19 patents with chronic disease have been shown to increase pro-inflammatory mediators IL-6 and these patients are at higher risk of serious complications of COVID-19.[14,15]

It is also believed that men have been shown to have been more at risk of developing thrombotic complications, and elderly patients are severely affected by the infection so they require ICU admission, and be higher incidence of thrombosis.[16]

Several mechanisms have been proposed for coagulation pathogenesis likely involves the following[17] (Figure 1):

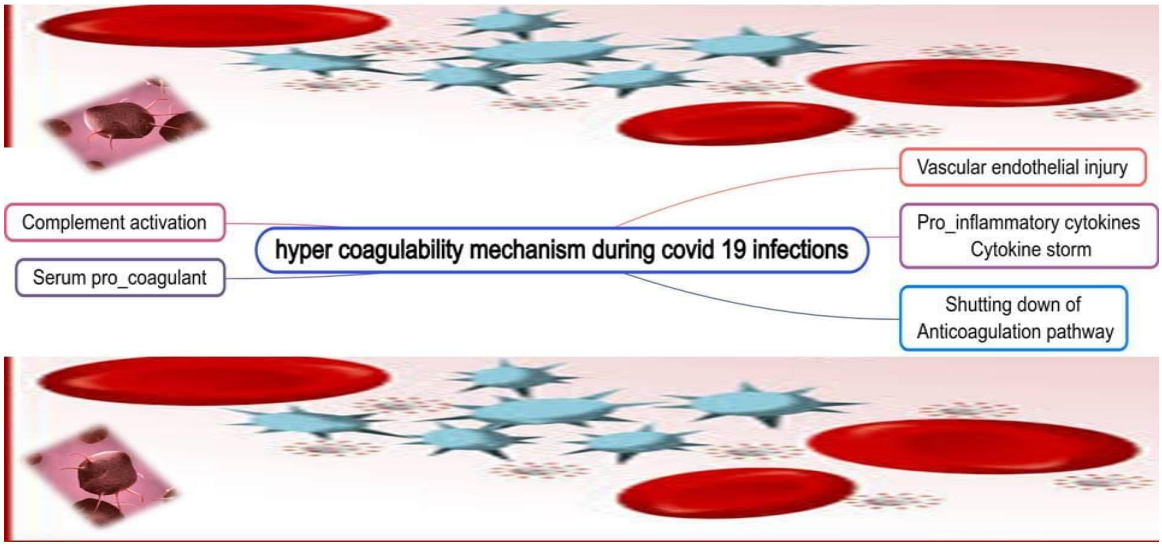

Figure 1. Mechanisms of Hypercoagulability-Related to COVID-19 Infection

The causal, bi-directional relationship between inflammation and thrombosis is well established. COVID-19 causes a profoundly pro-inflammatory state, as evident from multiple reports of high C-reactive protein, lactate dehydrogenase, ferritin, interleukin-6 and D-dimer levels. IL-6 and fibrinogen levels are shown to correlate with each other in COVID-19 patients, providing credence to the idea of inflammatory thrombosis,[18] and excessive cytokine release contributes to thrombosis through multiple mechanisms, including activation of monocytes, neutrophils, and the endothelium, all of which generates a prothrombotic state like increasing production of IL-6, IL-7, TNF, and inflammatory chemokine's such as

CCL2, CCL3, and soluble IL-2 receptor.[19] The immune system and homeostasis complement each other in order to defend against a pathogen. This physiological mechanism could be dysregulated, leading to the formation of excess thrombus formation, when infected with COVID-19.[20] It has also been suggested that the virus itself play role in activation the coagulation cascade.[21] As for the neutrophil count, lymphocyte count, and platelet count correlate with disease severity.[22]

There are many changes to be made in this case include: increased fibrinogen concentration, increased factor VIII activity, increased circulating von Willebrand factor, elevated D-dimer, cardiac troponin, ferritin, lactate dehydrogenase, and IL-6 levels, prolongation of the prothrombin time, and exhausted fibrinolysis.[23,24]

Etiology of Hyper-Coagulability after Vaccination Against COVID-19

Thrombosis symptoms are observed in many COVID-19 vaccinated recipients. It is found that all vaccines can lead to this problem, but greatly it is noticed in AstraZeneca and Johnson vaccine.[25-27] Cerebral venous sinus thrombosis (CVST) with thrombocytopenia has been recorded in patient receipt adenoviral vector vaccine.[28] European Medicine Agency's Pharmacovigilance Risk Assessment Committee, show that" 169 cases of cerebral venous sinus thrombosis and 53 cases of splanchnic vein thrombosis were reported, from the 34 million people who takes the AstraZeneca COVID-19 vaccine in the first two weeks of getting vaccinated.[25] Moreover, some reports of venous thrombosis after vaccination with Johnson vaccine are recorded.[26]

This problem was found to be rare, that makes the benefits of the vaccine overcome the risks. As a consequence, Vaccination against covid-19 remains critical for control of this pandemic problem.[29] Laboratory results of patients with thrombosis after receiving the vaccine were as following: high level of D-dimer, low platelet count, low fibrinogen and high levels of IgG antibodies against PF4 complexes.[30,31] Scientists were not able to reach a clear cause for the occurrence of clots, but many hypotheses have been developed about this aspect (Figure 2).

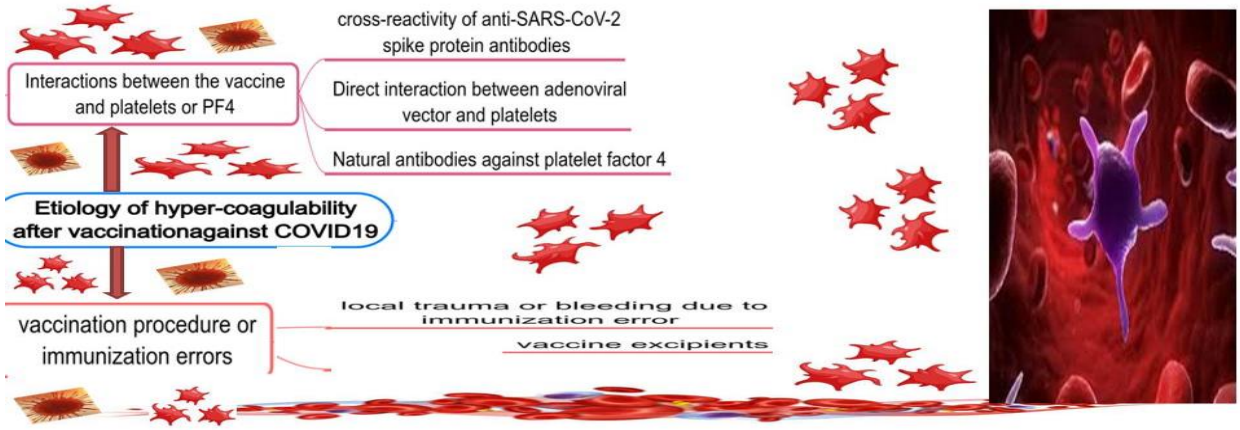

Figure 2. Mechanisms of Hypercoagulability after Vaccination Against COVID-19 Infection

The type of carrier and the components of the vaccine play a major role in the occurrence of clots after receipt the vaccines. AstraZeneca COVID vaccine and Johnson vaccines composed of replicating adenoviral vectors.[28,35] Interactions between the vaccine and platelets or platelet factor 4 (PF4) play a major role in the pathogenesis of VACCINE Induced immune thrombotic thrombocytopenia (VITT).[29,32] The direct interaction between adenoviral vector and platelets in which the free DNA in the vaccine binds to PF4 and triggers platelet-activating immunoglobulin G (IgG) antibodies.[27,32,33] Anti-PF4 binds to PF4 complexes that forms immune complexes bind to Fc-receptors on platelets (FcγRIIA).[27,33] This causes platelet activation and appearance of platelet micro fragments of that initiate clotting formation stimulates prothrombotic cascade and decreases platelet count that causes thrombocytopenia.[32]

Activation of the clotting cascade results in thrombosis generation and increases the risk for new thrombosis.[33] Polymorphisms in FcγRIIA were found to have a great role in this cascade.[32,33] Cross-reactivity between anti-SARS-CoV-2 spike protein antibodies

with PF4 also can occur.[34] Cross-reaction between the vaccine, platelets, and PF4 has also been considered as a contributing factor since adenovirus can bind to platelets resulting in platelet activation.[35] In addition, platelets express high levels of the angiotensin-converting enzyme-2 to which Spike protein binds.[36] As a consequence, vaccine Spike protein may directly activate platelets, initiating clotting pathway.[34] Presence of natural IgG antibodies against (PF4) also contribute to platelet activation as that bind PF4 complexes and result in platelet activation.[37,38] Another opinion on this aspect is showed by McGonagle and coll that how cerebral sinus- and splanchnic veins make it possible for viral products that present in body fluid to reach the endothelial layers of different vessels.[39] These sites have a high amount of anti-PF4 autoantibodies that interact and activate of platelets, as mentioned previously.[40] Another hypothesis has been established forward by some scientists on these mechanisms that the defect may be in vaccination procedure or immunization errors.[41] In normal situation, the component of the vaccine must reach to the cell nucleus not to cell fluids. Most vaccines are given *via* the intramuscular route,[39] any suddenly local trauma or bleeding due to immunization error can lead to escapation of vaccine component and appearance of extracellular DNA, which may act as a strong stimulant for local immune response.[39,40] Widespread distribution of viral vectors in blood stream in which many interactions between these vectors, platelets and blood component can happen.[42] As mentioned earlier, the components of the vaccine have a role in this issue, as it contains preservatives, or stabilizers (also known as excipients) that stimulate the immune system in a rare and excessive response, leading to clots[41]. Andreas Grenache, and his team in the German University of Grief's Weald, pointed that Preservatives material in vaccine interact with proteins in the body which are responsible in clots formation.[43] The German team examined more than 1,000 proteins in the AstraZeneca vaccine, in addition to a preservative known “ethylene diamine tetra acetic acid, which is known to cause structural, biochemical and functional injury to blood platelets alongside clotting formation.[44] These proteins spread in the bloodstream, and they interact with platelets or "PF4" to form compounds that activate the production of antibodies that recognize PF4 as mentioned before.[43]

Use of Anticoagulants and Antiplatelet Agents During Infection and After Vaccination

The management of hypercoagulability in COVID-19 can be challenging due to limited data. So, unfortunately, there is no solid scientific evidence to support antithrombotic therapy in patients infected with COVID-19 or receive its vaccine. Although there is no specific drug to treat SARS-CoV-2, a number of drugs are under investigation and have been made available for using in clinical practice.[45] Research and studies are still in progress. In a pre-proof retrospective study of 2773 patients hospitalized with COVID-19, patients who received anticoagulation (786 patients, 21%) had an in-hospital mortality rate of 22.5% and a median survival of 21 days, compared with 22.8% and a median survival of 14 days in those who did not receive anticoagulation.[46] Many drugs after several experiments conducted on it, have been used to treat clotting during infection with the Corona virus or after taking its vaccine to keep up with the possible complications of this vaccine, these drugs include anticoagulant and antiplatelet drugs. There are recommendation further clinical trials to evaluate the safety and efficacy of combining antiplatelet and anticoagulants agents in the management of COVID-19 patients, and recommend administration of anticoagulants varying in doses based on case severity in COVID-19 patients.[47,48]

Low-dose aspirin is an inexpensive drug with an anti-inflammatory, antithrombotic effects, and antiviral properties against RNA viruses.[49,50] Using low-dose of aspirin in COVID-19 patient showed effective results in secondary prevention of Atherosclerotic Cardiovascular Disease (ASCVD) alongside decreasing the risk of ICU admission and mechanical ventilation in hospitalized patients who take prehospital low-dose aspirin therapy.[51] Aspirin use found to be associated with improving outcomes in hospitalized COVID-19.[52] A recent cohort study in Denmark involved 9236 confirmed COVID-19 patients with (2.7%) nonsteroidal anti-inflammatory drugs (NSAID) user therapy (aspirin is a type of NSAID), indicates that using of NSAIDs was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation or renal replacement therapy in Danish patients who tested positive for COVID-19.[53]

Several pharmacological effects of aspirin have been postulated to have clinical applications in the modulation

of inflammatory pathways, thrombosis, and viral infectivity. Low-dose aspirin has pleiotropic effects with potential benefits especially early in the course of COVID-19 illness.[54] Firstly, irreversible inhibition COX-1 enzyme which inhibits the synthesis of thromboxane A_2 resulting in inhibition of platelet aggregation and potent anti-thrombotic action.[54] Inhibition of platelet activation lead to suppression of release reaction followed by inhibition of neutrophil recruitment on vascular endothelium and reducing of thrombin generation.[55] Secondly, acetylation of COX-2 enzyme leads to synthesis of resolvins that promote resolution of inflammation induced by tissue damage and cytokines in COVID-19.[56] Aspirin can control the acute respiratory distress syndrome (ARDS) process. Zhou et al said that administration of aspirin before getting hospitalized can prevent severe ARDS and decrease serious COVID-19 complications.[57] This can be occurred by Inhibition the enzyme COX and preventing the formation of pro-inflammatory thromboxane and prostaglandins.[58] This cause Inhibition of the release of nuclear factor kappa B (NFκB) from its inhibitor IkB and preventing the formation of pro-inflammatory cytokines and chemokines leading to the production of aspirin triggered lipoxin that induces the release of endothelial nitric oxide and inhibits production of IL-8 and myeloperoxidase which followed by restoration of neutrophil apoptosis and promotion of resolution.[58] Consequently, Increasing the production of nitric oxide (NO) and resulting in reduced migration and infiltration of neutrophils and endothelium permeability.[58] American Diabetes Association state that Aspirin therapy (75-162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding.[59]

Dipyridamole (2-6-bis(diethonolomino)-4,8-dipiperidino-pyrimido 5,4-d-pyrimidine) has lately being used as a coronary vasodilator and inhibitor for platelets aggregation after 50 years of producing it.[60] The antiplatelet agent Dipyridamole act as phosphodiesteradse (PDE) inhibitor but increase intracellular adenosine 3,5- monophosohate (cAMP)/cyclic guanosine 3,5-monophosphate (cGMP).[60] Hence,rise in cAMP that inhibit platelet aggregation lead to control the adenosine-mediated activation of platelet adenosine A2A receptors(A2AR).[61] it also suppress the reuptake of adenosine but red blood cell, so it increase plasma level of this vasodilator and platelet inhibitor nucleoside.[60] Moreover, it acts as antioxidant by scavenging free radicals that inactivate cyclo-oxygenase, by this way inhancing prostaglandin I 2(PGI2) biosynthesis.[60,62,63] Dipyridamole effect in SARS-COV-2 replication in vitro and inhibit it as reported recently, also, adjunct dipyridamole can inhance the clinical course in sever COVID-19.[64] And boosting clinical outcomes, since dipyridamole (DIP) therapy led to increased circulating lymphocyte and platelet counts and lowered D-dimer level.[65] DIP has broad spectrum antiviral activity as it suppresses inflammation and promotes mucosa healing.[66,67] It was found that DIP adjunctive treatment was effective in preventing hypercoagulability if applied early in the severe COVID-19 patients.[65]

Clopidogrel is anti-platelet that contributes in reducing coagulation by prevents platelet activation and aggregation this help patients from death after COVID-19 infection. Clopidogrel is a new thienopyridine derivative, which inhibits adenosine diphosphate-induced platelet aggregation.[68] It prevents platelet activation and aggregation by irreversibly inhibiting the P2Y12 class of adenosine diphosphate (ADP) receptors on the surfaces of platelets and this irreversible binding prevents activation of platelet surface GPIIb/IIIa receptors thus preventing the platelets ability to bind fibrinogen.[69] Sometimes, you may be given both low dose aspirin and clopidogrel they are very effective.[70] there are studies proved use clopidogrel with aspirin is very active from use it alone.[71] Clopidogrel is active only after intravenous or oral administration.[72] It uses to prevent arterial thrombotic events and decrease mortality rate in patients with COVID-19. Before taking clopidogrel, the patient should be sure to tell his doctor and pharmacist about all prescription, over-the-counter, and other drugs he takes. Also, he should tell them about any vitamins, herbs, and supplements he uses.

Heparin is a polysaccharide originally isolated from mammalian animal tissue in 1916.[73] Heparin was the first true anticoagulant.[74] It comes in two forms: Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Both UFH and LMWH have

the ability of binding to anti-thrombin (AT) glycoprotein, enhancing AT inactivation of potent enzymes in the coagulation pathway, such as Factor Xa and Factor IIa (Thrombin).[74] In other words, it acts by promoting formation of an intermediate protease-heparin-anti thrombin complex which facilitates inhibition of thrombin and activated factor x.[75]

Considering the findings that the antiviral effect of UFH could be stronger than LMWH, the dose of choice must be decided carefully, once UFH presents a higher risk for bleeding than LMWH. It was noticed in a published research that heparin sulfate (HS) derivatives, such as UFH and LMWH, at feasible concentrations for clinical application, induces conformational alteration of the SARS-CoV-2 Spike protein which is a central molecule for the host's cell invasion.[75] The advantageous of heparin underlying treatment of COVID-19 patients could be explained not only by its anticoagulant properties but also due to its non-anticoagulant mechanisms, which include anti-viral and anti-inflammatory actions such as decrease of COVID-19 host cell entry, inhibition of pro-inflammatory cytokines and chemokines, inhibition of vascular permeability and leukocyte migration.So, WHO recommended in COVID-19 patients thrombo-prophylaxis with either UFH or LMWH.

Low molecular weight heparin or unfractionated heparin is preferred over oral anticoagulants to critically ill patients; because the two types of heparin have shorter half-lives, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions. Alternative therapy should be considered in patients with contraindications for heparin, such as heparin-induced thrombocytopenia or active or recent bleeding.

A possible explanation for the failure of heparin to properly inhibit or reduce coagulation in COVID-19 patients could be the development of heparin resistance in a select group of patients suffering from aggravated disease status. Patients prone to heparin resistance commonly present with a deficiency in antithrombin III, increased fibrinogen and D-dimer level 76. It can result from increased heparin-binding protein levels, low ATIII levels, increased heparin clearance levels, high factor VIII levels and factitious resistance.[77]

Warfarin is the most commonly used oral anti-coagulant; whereas the most commonly used anti-platelet medications include aspirin and clopidogrel, each of which influences blood hemostasis through different mechanisms. It makes your blood flow through your veins more easily and decrease a dangerous blood clot. Warfarin has a relatively narrow therapeutic index around which under-dosing may result in recurrent thrombosis and over-dosing may result in severe and life-threatening bleeding.[78] Warfarin exerts its anticoagulant effect by inhibiting vitamin K production, which is essential for the metabolism of certain coagulation factors.[79] It has an initial pro-thrombotic effect, by initially blocking proteins C and S, followed by a delayed antithrombotic effect, through the inhibition of coagulation factors II, VII, IX, and X.[80] If you are taking warfarin, it is important to be consistent with what you eat and drink because this may affect how well this medicine works. It's usual to take warfarin once a day, normally in the evening and Regular measurement of International Normalized Ratio (INR) levels is an essential component in the management of patients receiving warfarin treatment. Warfarin is very important for patients that suffer from coagulation after COVID-19 infection or COVID-19 vaccines.

Direct Oral Anticoagulants (DOACs)

These agents are used to treatment and prevention deep vein thrombosis and pulmonary embolism that made after COVID-19 infection. It is drugs are now standard of treatment in venous thrombosis and atrial fibrillation. DOACs are target-specific anticoagulants that inhibit both free and bound activated serine proteases.[81] Also, DOACs directly, selectively, and reversibly inhibit factors IIa or Xa.[82] There are many anticoagulants including one direct thrombin inhibitor (dabigatran) and three factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban).[83] Dabigatran direct thrombin inhibitor by inhibiting active thrombin (factor IIa) that prevents the conversion of fibrinogen to fibrin and inhibits free thrombin.[84] Rivaroxaban is a direct inhibitor of factor Xa that decreases thrombin concentration and reduces the risk of blood clots forming in the veins and arteries.[84] Rivaroxaban inhibits both the intrinsic and extrinsic coagulation cascades because it blocks the enzyme involved in the production of thrombin.[84] Apixaban (Eliquis) is a potent and direct inhibitor of FXa that specifically and reversibly inhibits both prothrombinase and clot-bound FXa.[85] The advantage of DOACs is that they do not require routine anticoagulation monitoring because it is wide therapeutic

index.[86] DOACs are very important in reducing coagulation that become after COVID-19 infection and protect patients from clotting that maybe happen in any place in your body. There are currently no clinical data on safety or efficacy of DOAC use in COVID-19 patients.[87] So, one must ask his doctor if he wants to take DOACs during COVID-19 infection. It reduces clotting in patients but not remove clotting completely.

Conclusion

The hypercoagulable state in COVID-19 is considered as emergent state since many major pathological events occurred with serious consequences related to mortality and morbidity. There are many evidences support that the hypercoagulabity which is caused by SARS-COV-2, includes a unique mechanism of thrombo-inflammation cascade that is triggered by viral infection and other ways. The therapeutic and vaccination intervention for thrombotic complications associated with the COVID-19 epidemic has also considered playing a major role in reducing the mortality and morbidity complications resulting from these clots. Regardless of some possible risks produced by vaccines, the benefits resulting from taking it outweigh the risks caused by it, so controlling the spread of this virus is the goal that is sought and requires the concerted efforts of all categories, competent, and non-competent authorities to score it.

Conflict of Interest

The authors declare no conflicts of interest.

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