Mini Review Article

The Role of Anticoagulants and Antiplatelets in Prophylaxis and/or Treatment of Sever SARS-CoV-2 Infection: Mini Review

Abstract

High incidence of thrombotic events was correlated with the severe acute respiratory syndrome coronavirus 2 (SARAS-COV-2). Exploring anticoagulants to be added as thromboprophylaxis for Covid 19 patients become a must. Many anticoagulants are available, however, there are factors controlling the use of thromboprophylaxis. Some of these factors mentioned in this mini-review.

Keywords:
Severe acute respiratory syndrome coronavirus-2(SARAS-COV-2), Fibrinolytics, Antiplatelets, Anticoagulants.

1. SARAS-COV-2 overview

The severe acute respiratory syndrome coronavirus 2 (SARAS-COV-2)or Covid-19 (Corona virus disease-19) was first reported in Wuhan, china by the end of 2019 then due to the high potential for dissemination it was reported by WHO as pandemic diseases in 2020.[1] The symptoms in people with (SARAS-COV-2) range from minor to severe symptoms. Fever, continuous cough and diarrhea are considered as a mild stage illness, however, some patients develop severe disease with pneumonia with dyspnea, tachypnea that requires hospitalization and oxygen support and other patients may develop respiratory dysfunction and disturbed gas exchange, shock or multiple (extra pulmonary) organ failure to an extent that require admission to intensive care as they develop a type of acute respiratory distress syndrome (ARDS).[2]

2. Coagulation disorders associated with SARAS-COV-2

From the beginning of this pandemic the focus was to find an effective antiviral and developing an effective vaccination to help in limiting the dissemination of this new virus and decrease the number of deaths. However, another cause of death in SARAS-COV-2non survivors was reported in retrospective cohort study which is coagulopathy or disseminated intravascular coagulation (DIC) with a decline in fibrinogen.[3] Giving a new road for the physicians to explore anticoagulants as another drug category away from antivirals that can be included in the treatment protocols for SARAS-COV-2.

Acute respiratory distress syndrome (ARDS) developed at the end stage of SARAS-COV-2 infection is associated with increased alveolar-capillary permeability and exudation of fluid containing albumin, fibrinogen, proinflammatory cytokines, and coagulation factors. This leads to propagate the local inflammatory response (cytokine storm) and fibrin deposition in the air spaces and lung parenchyma that contribute to subsequent alveolar fibrosis. Thrombosis and inflammation are two processes that mutually reinforce each other. Recent case studies describe fibrin deposits in biopsies of lung tissue from patients with COVID-19 with ARDS commonly reported. So targeting the fibrinolytic system to promote fibrin resolution could limit severity and improve pulmonary function.[4, 5]

3. Anticoagulants ' role in SARAS-COV-2 management

After coagulopathy findings, many recommendations suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation.Moreover, coagulation laboratory test should be made at for all patients with COVID-19, especially: D-dimer, prothrombin time, and platelet count.[6]

Anticoagulants now are included in most of the guidelines and protocols for the management of COVID-19 patients, however, individualized strategy should be followed among some special cases. Some patients may progress to a hypocoagulable phenotype when fibrinogen levels begin to decrease. At this point anticoagulants intake should be stopped.[7, 8] Oral anticoagulants (OAC) are associated with many side effects and drug-drug interactions so they are not recommended in case of Covid-19.The most commonly used anticoagulants for Covid-19 patients is Heparin. The use of heparin has potential benefit over other anticoagulants due to its anticoagulant, anti-inflammatory in addition its potentially anti-viral properties through acting on SARS-CoV-2 surface receptor binding proteins and inhibiting viral attachment.[9, 10]

All COVID-19 hospitalized patients with should be placed on prophylactic doses of anticoagulation either Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) according to the clinical case of the patients during admission.[11] Also, LMWH or UFH may be preferred in critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants. Venous thromboembolism, pulmonary embolism, and renal insufficiency are associated with LMWH so, UFH may be a preferred. Unfortunately, failure in anticoagulation response may occur in some patients that could be due to antithrombin-III deficiency and high levels of fibrinogen showed in Covid-19 patients.[12] Also, heparin will prevent further fibrin deposition but will be ineffective in the removal of pre-existing fibrin.[13] However, tissue plasminogen activator (tPA)- a fibrinolytic agent- was reported to be used in refractory cases of hypoxia, demonstrating improvement during prolonged infusions in small case series, however, tPA use requiring more clinical studies.[14]

4 .Antiplatelets' role in SARAS-COV-2 management

Early antiplatelet therapy may be beneficial due to their inhibitory effects on platelet activation and generation of neutrophil-platelet aggregates, key mechanisms in both thrombus formation and pulmonary inflammatory responses. oral $P2Y_{12}$ inhibitor: ticagrelor confers more potent anti-inflammatory properties and potent antiplatelet effect and recommended to be used in Covid 19- patients. [15]

The combination between a platelet inhibitor to UFH or LMW heparin would increase the potential for risk for bleeding.[16]The early use of aspirin in covid-19 out patients, which has the effects of inhibiting virus replication, anti-platelet aggregation, anti-inflammatory and anti-lung injury, is expected to reduce the incidence of severe and critical patients, shorten the length of hospital duration and reduce the incidence of cardiovascular complications. However, clinical trials on Covid-19 patients are still enrolled and WHO has warned against self-medicating for COVID-19 any drug should be given according to evaluation of the patient situation.[17]

The following table summarizes the previously mentioned data related to the Thromboprophylaxis in 3 types of patients.[18]

Out patients	Hospitalized patients	Post-discharge
Clinical and laboratory data should be monitored		
Thromboprophylaxis not recommended due to possible side effects in absence of venous thromboembolism (VTE) However, some studies recommend Antiplatelet use under medical supervision and according to the patient medical history and situation	Thromboprophylaxis is strongly advised during the staying period.	Thromboprophylaxis should be maintained for 7-14 days after hospital discharge
	Doses and type of Thromboprophylaxis should be tailored according to the patient medical situation with close monitoring	

Methods:

The review was performed using **PubMed** to identify relevant articles published.

Conclusion

Severe acute respiratory syndrome coronavirus 2 (SARAS-COV-2) is associated with severe cytokine storm and coagulopathy which participate in the patients' response to the infection. Antivirals are not the only therapeutic approaches; other drug categories may be included in the treatment protocol. Despite the improvement of most cases received anticoagulant therapy, this category of drugs could not be used as a standard therapy for all Covid-19 patients. Till today we have no idea about what is hidden beyond SARAS-COV-2. No current medicine that can effectively treat the disease .More investigation about the drug pathophysiology is required and exploration of all potential therapeutic approaches is mandator

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