THE ROLE OF ANTICOAGULANTS AND ANTIPLATELETS IN PROPHYLAXIS AND/OR TREATMENT OF SEVERE SARS-COV-2 INFECTION

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ABSTRACT
Severe acute respiratory syndrome coronavirus-2 (SARAS-COV-2) was reported firstly in China by the end of 2019 then disseminated vigorously worldwide and in 2020 reported by WHO as pandemic disease. It is associated by many symptoms, however, high incidence of thrombotic events was strongly correlated with SARAS-COV-2. Exploring anticoagulants to be added as thromboprophylaxis for Covid 19 patients become a must. Many options for thromboprophylaxis are available including anticoagulants, antiplatelets and fibrinolytics which were illustrated in this mini review.

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

INTRODUCTION
SARAS-COV-2 overview
The severe acute respiratory syndrome coronavirus 2 (SARAS-COV-2) or Covid-19 (Corona virus disease-19) was reported firstly 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. 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, tachyplea 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 progress to a type of acute respiratory distress syndrome (ARDS). 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-2 non survivors was reported in retrospective cohort study which is coagulopathy or disseminated intravascular coagulation (DIC) with a decline in fibrinogen. 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. The acute respiratory distress syndrome (ARDS) developed at SARAS-COV-2 infection end stage is associated with increased alveolar-capillary permeability with exudation of fluid containing albumin, fibrinogen, proinflammatory cytokines, and coagulation factors. This leads to propagate the local inflammatory response (cytokine storm) and fibrin overthow in air spaces and lung tissues that contribute to subsequent alveolar fibrosis. Thrombosis and inflammation are two procedures that reciprocally reinforce each other. Fibrin deposition in lung tissue biopsies from patients with COVID-19 with ARDS were reported in recent case studies. Thus, the fibrinolytic system could be a target to promote fibrin resolution, limit the severity and improve pulmonary function. Anticoagulant's role in the management of SARAS-COV-2
After coagulopathy findings, many guidance suggest that all COVID-19 hospitalized patients should receive...
thromboprophylaxis, or full intensity anticoagulation therapy. Moreover, coagulation laboratory test should be made at for all COVID-19 patients, especially: D-dimer, prothrombin time or activity and platelet count⁹. Anticoagulants now are included in most of the recommendations and protocols for COVID-19 patient’s management; however individualized strategy should be followed among some special cases. A hypocoagulable phenotype may develop in some patients when fibrinogen levels begin to decrease. At this stage anticoagulants intake must stopped⁹,⁸. 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 possible benefit of heparin over other anticoagulants is its anticoagulant, anti-inflammatory properties, in addition its potential anti-viral activity through acting on SARS-CoV-2 surface receptor binding proteins and inhibiting viral attachment⁸,¹⁰. Prophylactic doses of anticoagulants either Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) must be given to all hospitalized COVID-19 patients according to the clinical case of the patients during admission¹¹. Also in critically ill COVID-19 patients, LMWH or UFH are preferred because of their shorter half-lives, intravenous or subcutaneous administration 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 patients¹². Also, further fibrin deposition will be prevented by heparin, but it is ineffective in the removal of pre-existing fibrin¹³. However, in refractory cases of hypoxia, tissue plasminogen activator (tPA)- a fibrinolytic agent- was used and showing improvement during prolonged infusions in small case series, despite that, tPA use requiring more clinical studies¹⁴.

| Table 1: Thromboprophylaxis in 3 types of patients¹⁸ |
|-------------------------------------------------------|
| **Clinical and laboratory data should be monitored**   |
| **Out patients**                                      | **Hospitalized patients**                                      | **Post-discharge**                        |
| Thromboprophylaxis not recommended due to possible side effects in absence of venous thromboembolism (VTE) | Thromboprophylaxis is strongly advised during the staying period. | Thromboprophylaxis would be maintained for 7-14 days after discharge from hospital |
| However, some studies recommend Antiplatelet use under medical supervision and according to the patient medical history and situation | | |

**Antiplatelets’ role in SARAS-COV-2 management**

Early starting antiplatelet therapy might be beneficial owing to their inhibitory effects on platelet activation and generation of neutrophil-platelet aggregates, key mechanisms in both thrombus formation and pulmonary inflammatory responses. Oral P2Y₁₂ inhibitor, ticagrelor confers more potent anti-inflammatory properties and potent antiplatelet effect and recommended to be used in Covid 19 patients¹⁵. The combination between a platelet inhibitor to UFH or LMW heparin would increase the potential for risk for bleeding¹⁶. Because it has the effects of inhibiting virus replication, anti-platelet aggregation, anti-inflammatory and anti-lung injury, the early use of aspirin in covid-19 out patients 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 situation¹⁷.

**METHODS**

The review was performed using PubMed, bioRxiv and cureus 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 that 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. There’s No current medicine that can effectively treat the disease. More investigation about the disease pathophysiology is required and exploration of all potential therapeutic approaches is mandatory.
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