Available online at *www.ujpronline.com*
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)
Copyright©2021; The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited

REVIEW ARTICLE

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

Wessam F. El-Hadidy[1], Asmaa A. Khalifa[*2]
[1]*Department of Pharmacology and Experimental Therapeutics, Medical Research Institute, Alexandria University.*
[2]*Department of Pharmacology and Therapeutics, Faculty of Pharmacy, Pharos University in Alexandria, Egypt.*

Article Info:

Article History:
Received: 1 December 2020
Reviewed: 5 January 2021
Accepted: 12 February 2021
Published: 15 March 2021

Cite this article
El-Hadidy WF, Khalifa AA. The role of anticoagulants and antiplatelets in prophylaxis and/or treatment of severe SARS-COV-2 infection. Universal Journal of Pharmaceutical Research 2021; 6(1):49-51.
https://doi.org/10.22270/ujpr.v6i1.540

***Address for Correspondence:**
Asmaa Ahmed Khalifa, Department of Pharmacology and Therapeutics, Faculty of Pharmacy, Pharos University in Alexandria, Egypt. Tel- +201093771967;
E-mail: *asmaa.khalifa@pua.edu.eg*

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[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 progress to a type of acute respiratory distress syndrome (ARDS)[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. 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 overthrow 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[4,5].

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 count[6]. 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 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 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 attachment[9,10]. 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 admission[11]. 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 patients[12]. Also, further fibrin deposition will be prevented by heparin, but it is ineffective in the removal of pre-existing fibrin[13]. 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 studies[14].

Table 1: 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 would be maintained for 7-14 days after discharge from hospital
	Doses and type of Thromboprophylaxis should be tailored according to the patient medical situation with close monitoring	

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 $P2Y_{12}$ 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]. 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 situation[17].

METHODS

The review was performed using PubMed, bioRxiv and cureus to identify relevant articles published.

CONCLUSIONS

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.

ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Pharos University in Alexandria, Egypt to provide necessary facilities for this work.

AUTHOR'S CONTRIBUTION

El-Hadidy WF: writing original draft, literature survey. **Khalifa AA:** methodology, formal analysis, conceptualization. Both authors revised the article and approved the final version.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

REFERENCES

1. Al-Qahtani AA. Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2): emergence, history, basic and clinical aspects. Saudi J Biol Sci 2020); 27(10):2531-8. *https://doi.org/10.1016/j.sjbs.2020.04.033*
2. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395.10223: 497-506. *https://pubmed.ncbi.nlm.nih.gov/31986264/*
3. Yang X, Yu Y, Xu J, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine 2020; 8 (5):475-81. *https://doi.org/10.1016/S2213-2600(20)30079-5*
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(4): 844 -7. *https://doi.org/10.1111/jth.14768*
5. Whyte CS, Morrow GB, Mitchell GL, *et al*. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost 2020;18(7):1548-55. *https://doi.org/10.1111/jth.14872*
6. Marietta M, Ageno W, Artoni A, *et al*. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfusion 18.3 2020; 18(3): 167-9. *https://doi.org/10.2450/2020.0083-20*
7. Thachil J, Tang N, Gando S, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18(5):1023-6.*https://doi.org/10.1111/jth.14810*
8. Kollias A, Kyriakoulis KG, Dimakakos E, *et al*. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. British J Haematol 2020;189(5): 846-7. *https://doi.org/10.1111/bjh.16727*
9. Paranjpe I, *et al*. Association of Treatment Dose Anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J American College Cardiol 2020; 76(1):122-4. *https://doi.org/10.1016/j.jacc.2020.05.001*
10. Jaillette E, Girault C, Brunin G, *et al*. French Intensive Care Society, International congress -Réanimation 2016. Annals Intensive Care 2016; 6(1): 50. *https://doi.org/10.1186/s13613-016-0114-z*
11. Mycroft-West C, Su D, Elli S, *et al*. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 receptor binding domain undergoes conformational change upon heparin binding. Bio Rxiv 2020. *https://doi.org/10.1101/2020.02.29.971093*
12. Turshudzhyan A. Anticoagulation Options for Coronavirus Disease 2019 (COVID-19)-Induced Coagulopathy. Cureus 2020;12(5): e8150.
13. Tang N, Bai H, Chen X, *et al*. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18(5): 1094-9. *https://doi.org/10.1111/jth.14817*
14. Wang J, Hajizadeh N, Moore EE, *et al*. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. J Thromb Haemost 2020; 18(7):1752-5. *https://doi.org/10.1111/jth.14828*
15. Iba T, Jerrold H, Marcel L, *et al*. Coagulopathy of coronavirus disease 2019. Critical Care Medicine 2020; 48(9):1358-64. *https://doi.org/10.1097/CCM.0000000000004458*
16. Zhou X, Li Y, Yang Q, *et al*. Antiplatelet therapy after percutaneous coronary intervention in patients with COVID-19: Implications from clinical features to pathologic findings. Circulation 2020:141(22): 1736-38. *https://doi.org/10.1161/CIRCULATIONAHA.120.046988*
17. U.S. National Library of Medicine (NIH). Protective Effect of Aspirin on COVID-19 Patients (PEAC). Maryland: NIH; 2020.
18. Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054-62. *https://doi.org/10.1016/S0140-6736(20)30566-3*