



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com



Letter to the Editor

Mechanisms of stroke and the role of anticoagulants in COVID-19



Among patients with COVID-19 comorbidities like cerebrovascular event and atrial fibrillation have been reported in less than 2% of patients.¹ Interestingly occurrences of new cerebrovascular events and atrial fibrillation have been also reported in patients with COVID-19. Irrespective of the onset, the presence of a cerebrovascular event has been reported to affect clinical outcome in COVID-19. Agarwal et al. had reviewed studies on the impact of prior CVD among patients with COVID-19. They reported an increase in severity of COVID-19 illness, among patients with CVD.² In another review, we reviewed 2 studies reporting new-onset cerebrovascular events among patients with COVID-19 and reported that the presence of CVD as evident by neuroimaging predicted disease severity.³

Patients with severe COVID-19 illness can present with multiple patterns of cardiac injury including acute myocardial injury, cardiogenic shock, heart failure, cardiac arrhythmias, and myocarditis. Among these, only acute myocardial injuries, shock, and heart failure have been shown to predict the occurrence of stroke and disease severity.¹

Aghamohammadi et al. have suggested that anticoagulants including enoxaparin and heparin have a mortality benefit in patients with COVID-19.⁴ The mechanisms that have been postulated to cause neurological injury, and cerebrovascular events in patients with severe COVID-19 are i) cytokine storm, ii) embolic event in the background of myocarditis, and arrhythmia, iii) hypoxia-induced ischemia and apoptosis, iv) thrombotic microangiopathy, v) coagulopathy and thrombocytopenia, vi) direct viral invasion.¹

Among these mechanisms, instituting or continuing anticoagulation would be crucial in patients with prior history of atrial fibrillation, and the presence of embolism. Therapeutic anticoagulation has been tried among patients with severe COVID-19 with elevated D-dimers levels.⁵ Randomized clinical trials showing mortality benefit in these patients are still lacking. In the meantime, the clinician needs to be aware of the potential risks of the therapy. A recent study reported the occurrence of intracranial hemorrhage among 33 COVID-19 patients on therapeutic anticoagulation for elevated D-dimer levels. These

patients were treated with unfractionated heparin, enoxaparin, and argatroban. Mortality was reported in 15.2% of these patients, which was attributed to the parenchymal hemorrhage causing mass-effect and herniation. Based on their findings, the authors recommended initial brain imaging, before the institution of anticoagulation in all patients with severe COVID-19.⁵

The newer oral anticoagulants have a proven advantage in terms of safety and efficacy when compared to warfarin in the general population. However, there is limited literature on the safety, efficacy, and interactions between most cardiac medications in patients with COVID-19. Multiple medications including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, steroids, hydroxychloroquine, antivirals, antibiotics have been proven to be noncontributory in COVID-19 related mortality.¹ We believe the role of anticoagulation in patients with COVID-19 illness should be individualized. Future studies should compare outcomes among patients with non-severe and severe COVID-19.

Ethical statement

The article doesn't contain the participation of any human being and animal.

Verification

All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

Patient consent

Not applicable.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

<https://doi.org/10.1016/j.jfma.2020.06.026>

0929-6646/Copyright © 2020, Formosan Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

References

1. Aghamohammadi M, Alizargar J, Hsieh NC, Wu SV. Prophylactic anticoagulant therapy for reducing the risk of stroke and other thrombotic events in COVID-19 patients. *J Formos Med Assoc* 2020;119:1230–1. <https://doi.org/10.1016/j.jfma.2020.05.005>.
2. Mishra AK, Sahu KK, George AA, Lal A. A review of cardiac manifestations and predictors of outcome in patients with COVID – 19. *Heart Lung* 2020. <https://doi.org/10.1016/j.hrtlng.2020.04.019> [published online ahead of print, 2020 May 3].
3. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature. *Int J Stroke* 2020 Apr;20. <https://doi.org/10.1177/1747493020921664.1747493020921664>.
4. Mishra AK, Sahu KK, George AA, Sargent J, Lal A. Cerebrovascular events in COVID-19 patients. *Monaldi Arch Chest Dis* 2020 Jun 10;90(2). <https://doi.org/10.4081/monaldi.2020.1341>. PMID: 32527073.
5. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, et al. Hemorrhagic stroke and anticoagulation in COVID-19. *J Stroke Cerebrovasc Dis* 2020:104984. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104984> [published online ahead of print, 2020 May 23].

Ajay Kumar Mishra*
Kamal Kant Sahu

*Department of Internal Medicine, Saint Vincent Hospital,
Worcester, MA, 01608, USA*

Amos Lal

*Department of Pulmonology and Critical Care Medicine,
Mayo Clinic, Rochester, MN, USA*

E-mail address: Lal.Amos@mayo.edu (A. Lal)

Jennifer Sargent

*Department of Internal Medicine, Saint Vincent Hospital,
Worcester, MA, 01608, USA*

*E-mail address: Jennifer.Sargent@stvincenthospital.com
(J. Sargent)*

*Corresponding author.

*E-mail addresses: Ajay.Mishra@stvincenthospital.com (A.
K. Mishra), kamalkant.sahu@stvincenthospital.com (K.K.
Sahu)*

17 June 2020