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Complications of COVID-19 and possible role of angiotensin converting enzyme inhibitors and anti-platelet medications in lowering the risk of COVID -19 infection

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Abstract

COVID-19, the worldwide pandemic which effected the entire health care system, particularly showed its ill effects on patients with many comorbidities. Among the COVID-19 patients admitted in hospital, are with cardiovascular diseases and hypertension where associated with increased risk of mortality. Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB) were used in the management of hypertension and these medications revealed their beneficiary actions in the conditions of COVID -19 with Hypertension. On the other hand, COVID -19 also lead to thromboembolic complications which also required Intensive Care Unit admission within patients representing a unique condition termed as Covid Associated Coagulopathy (CAC). The impact of dual anti-platelet therapy reduced the risk of mechanical ventilation, ICU admission and mortality rate among individuals effected by Covid.

Keywords: Cardiovascular diseases; Thromboembolic diseases; Covid Associated Coagulopathy; Angiotensin converting enzyme inhibitors; Angiotensin receptor-II blockers; Anti-platelet therapy

1. Introduction

COVID-19 has placed significant onus on the health care systems worldwide, affecting patients with many comorbidities very severely in patients suffering particularly with cardiovascular diseases. The statistical analysis indicate 10.5% of fatal cases with cardiovascular diseases and 6% in patients with severe hypertension [1]. Most patients with cardiovascular comorbidities are treated with Angiotensin converting enzyme inhibitors and Angiotensin receptor-II blockers [2]. Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) uses the receptor Angiotensin converting enzyme-2 (ACE) for the entry into the target cells [3]. Among patients with COVID-19 admitted in hospital, the emerging data indicate that hypertension also may be associated with an increased risk of mortality due to COVID-19 [4, 5, 6].

The important data obtained from the patient demographic information, medical history, clinical characteristics, laboratory data, radiological report data, history of comorbidities and therapeutic interventions during the hospitalization and clinical outcomes were considered. The patient demographic information and clinical characteristics include age and gender, fever, cough, fatigue, dyspnea, heart rate, respiratory rate and blood pressure. The radiological report data and laboratory data like blood cell count, C- reactive protein, calcitonin, D-dimer and organ function markers were considered. Comorbidities like hypertension, coronary heart diseases, chronic renal diseases, cerebrovascular diseases, chronic liver diseases and chronic obstructive pulmonary disorder were extracted from medical history [7].

The objective of this article is to understand the different complications associated with covid-19 and studying the beneficial actions of Angiotensin converting enzyme inhibitors and Anti-platelet therapy in bringing down the mortality rate.

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2. Role of Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor-II Blockers (ARB)

Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB) are considered as first line medications for the management of large proportion of patients with severe hypertension [8, 9] . The Angiotensin converting enzyme inhibitors are designed to prevent the conversion of Angiotensin-I to Angiotensin-II and Angiotensin converting enzyme 2 further converts Angiotensin-II to Angiotensin-I-VII which counterbalance for the pro-inflammatory Angiotensin-II. When the virus occupies all the Angiotensin converting enzyme 2 receptors on the host cells, there is more Angiotensin-II free flowing in the system to activate the Renin Angiotensin System pathway (RAS), which leads to COVID-19 complications. If the conversion of Angiotensin-I to Angiotensin-II is blocked by Angiotensin converting enzyme inhibitors (ACEI), the COVID-19 complications will be prevented [10].

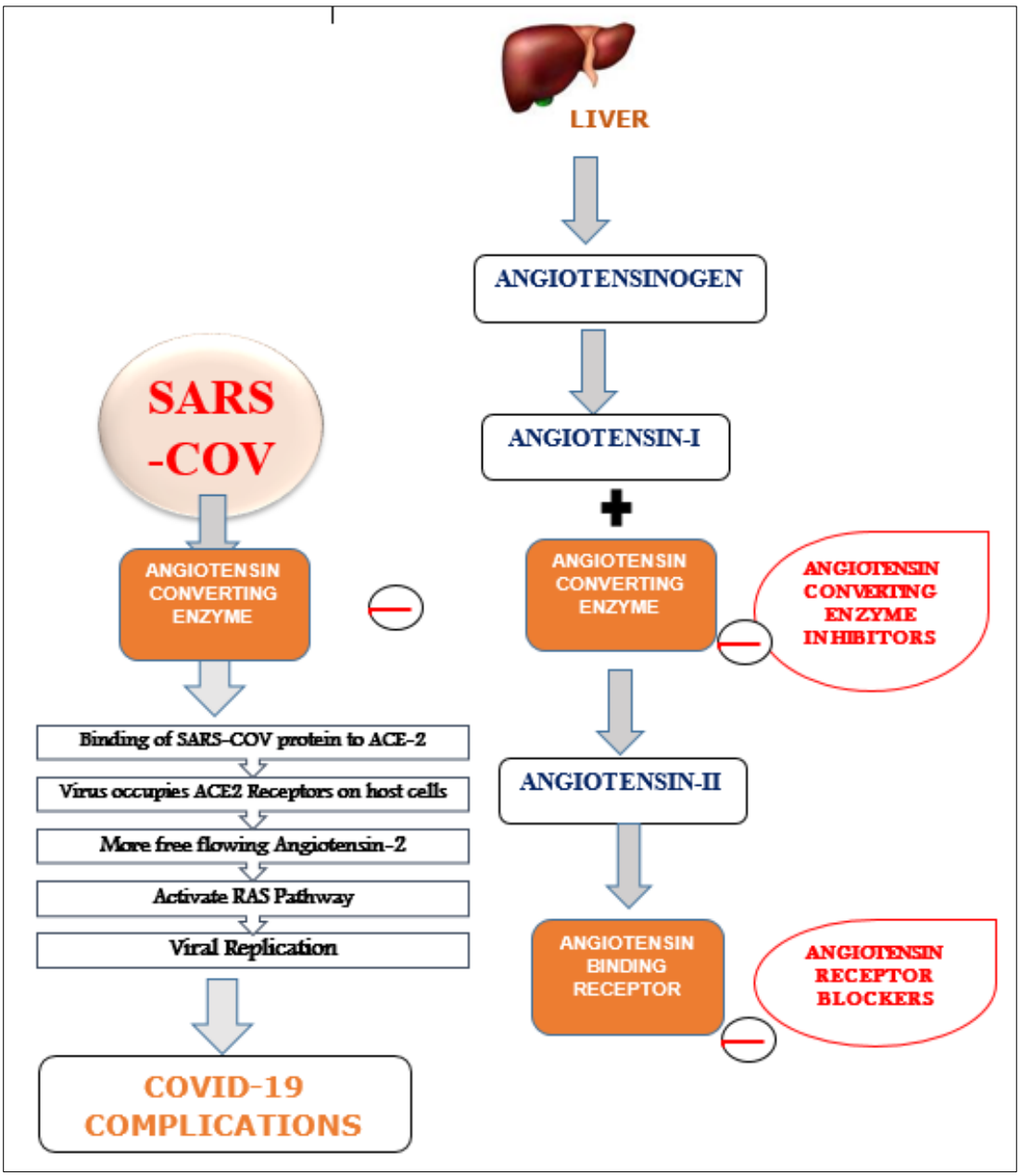

Figure 1 Intervention of SARS-COV on regular physiology of Renin Angiotensin System pathway and Mechanism of Action of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor–II Blockers

However, the continued usage of Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB) has become controversial in the setting of COVID-19, due to the fact that Angiotensin converting enzyme

inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB's) may increase the expression of Angiotensin converting enzyme 2 receptors in animal based studies [11, 12] , which is the known cellular receptor for Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection [13]. Conversely, it was indicated that Angiotensin converting enzyme 2 (ACE-2) down-regulated Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection, resulting in excessive activation of Renin Angiotensin System pathway (RAS) and exacerbated pneumonia progression [14]. Therefore, several case studies revealed that, there is a benefit in reference to administration of Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB's) by blocking Angiotensin converting enzyme 2 (ACE-2) down-regulation induced hyper activation of Renin Angiotensin System pathway (RAS) [7]. There is a lack of sufficient clinical data with reference to harmful effects of Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB's) use in patients with COVID-19 for the management of hypertension. COVID-19 is very uncertain and the exact mechanism remains to be established. Regardless of many deliberations, it was emphasized that several older patients on Renin Angiotensin System blockage because of latent or left ventricular dysfunction and that discontinuation of Angiotensin converting enzyme inhibitors (ACEI) may exacerbate heart failure [15].

It is also suggested that COVID-19 patients who are on treatment with Angiotensin converting enzyme inhibitors (ACEI) and Angiotensin receptor-II blockers (ARB's) should continue these medications as they may have many beneficial effects and these patients do not develop hypotension and acute kidney injury [16].

In conclusion, cardiovascular disease, hypertension and/ or their therapy by effecting Angiotensin converting enzyme 2 (ACE-2) levels may play very important role with regard to infectivity of COVID-19.

3. Role of Anti-Platelet Therapy

COVID-19 induced hypercoagulatory state that frequently leads to thromboembolic complications, whereas anti-coagulation is associated with reduced mortality and role of anti-platelet therapy is very less clear [17]. It is very evident that anti-platelet therapy might be effective in improving the ventilation in COVID-19 patients with severe respiratory failure. The effects might be sustained by the prevention and interference on formation of clots or thrombus in long capillary vessels and by modulating megakaryocytes function leading to platelet adhesion [18].

Thromboembolic complications are very common with patients reporting several incidences ranging from 7-45% with higher rates in critically ill patients who also require intensive care unit (ICU) [19-23]. The hypercoagulatory state induced in COVID-19 shows clinical and laboratory features with partially overlapped bacterial sepsis induced coagulopathy (SIC) but represents a unique condition that has been termed "COVID Associated Coagulopathy" (CAC) [24] which is characterized by wide spread deregulation coagulation parameters such as D-dimer, prolonged prothrombin time and slight reduction in platelet count [25]. The precise mechanism of COVID Associated Coagulopathy (CAC) is under investigation and seems very complexed due to several patho-physiological environmental conditions created by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection which is influenced by plethora of mediators [17]. Immunothrombosis represents crucial link with hypercoagulability, endothelial dysfunction, severe respiratory failure wherein neutrophils, platelets are dysregulated in coagulation cascade work [26-28].

Platelet derived Thromboxane A2 has vasoactive as well as prothrombotic properties [29]. Moreover, it is suggested that Thromboxane A2 might have a role in mediating the vasoconstrictor response of soluble fibrin in septic conditions [30]. Non- steroidal anti-inflammatory agents decreased the platelet adhesiveness by interfering with platelet prostaglandin synthesis such as Thromboxane A2 metabolite, partially restoring vasoplegic pulmonary regions and thus promoting an overall improvement in lung perfusion. [29]. Anti-coagulants and Fibrinolytic agents have been contemplated for the COVID-19 patients with coagulopathy [31, 32].

The impact of anti-platelet therapy on COVID-19 severity is currently unclear, whereas dual anti-platelet therapy improves hypoxemia [33], reduces the risk of mechanical ventilation, intensive care unit (ICU) admission and mortality without increasing the bleeding risk [34, 35].

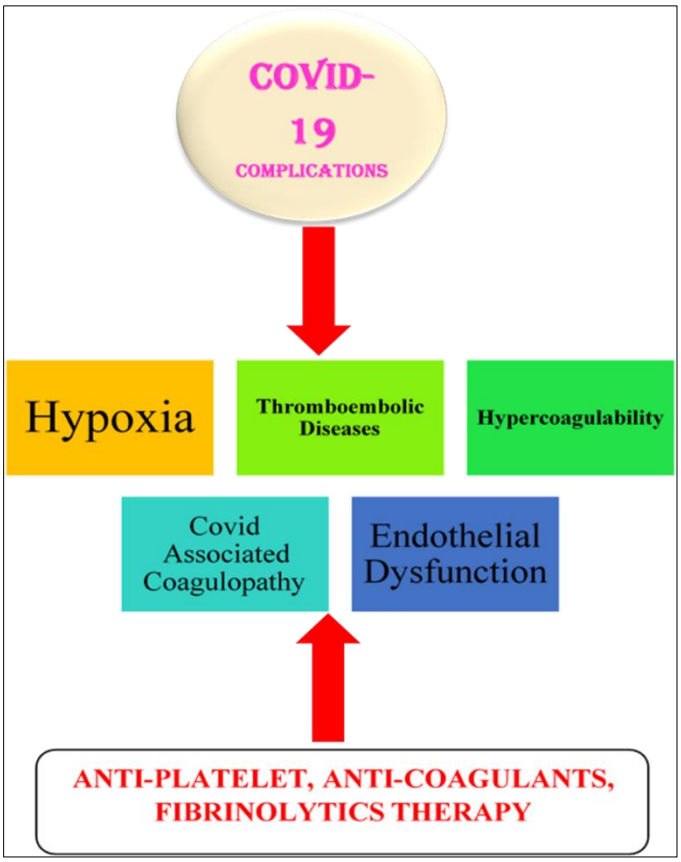

Figure 2 Complications associated with COVID-19 and different Drug Therapies

4. Conclusion

It is been concluded that due to the role exerted by Angiotensin converting enzyme inhibitors (ACEI) it can be proposed for the patients of COVID-19 to continue these medications as it is associated to bring down the possibility of mortality. The influence of anti-platelet therapy on COVID-19 severity is presently vague but it is shown to ameliorate hypoxemia, lessen the likelihood of mechanical ventilation, intensive care unit (ICU) admission and the threat of mortality.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors K Ravishankar, K Gnaneswari and K Sruthi, at the time of writing the article were employees of Aditya College of Pharmacy, Surampalem, India. The authors confirm that this article content has no conflict of interest.

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