Research Article

The Proposed Quadrable Positive Outcomes of Propranolol as Renin Inhibitor, Red Blood Cell Invasion Inhibitor, Cardiovascular Complications Mitigator, and Anti-Catabolizer in Management of Complicated Covid-19 Infection

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Abstract: Coronavirus disease (COVID_19) is an emerging respiratory virus. The World Health Organization (WHO) declared COVID-19 a global pandemic. Health professionals are looking forward to effectively and safely treat the infected patient by drug repositioning or to develop a vaccine and prevent the contagion. Recently, researchers tried to find a treatment for COVID-19 ,such as hydroxychloroquine . HCQ have side effects as Gastrointestinal upset (vomiting and diarrhea), Patients with long-term exposure to HCQ suffer from severe side effects, such as retinopathy, circular defects (or bull's eye maculopathy) , HCQ are metabolized in the liver with renal excretion of some metabolites, hence they should be prescribed with care in people with liver or renal failure, there is raise concerns about reports of COVID-19 causing liver and renal impairment, which may increase the risk of toxicity of HCQ when it is used to treat COVID-19. this problem leading us to looking for a safer alternative. The treatment of COVID-19 still not optimize, depending on treating symptoms or the complication patient develops and monitoring. Also, considering risk factors for the disease. Propranolol is the best alternative for HCQ as an effective and safe drug. At this review we have suggested propranolol which is a nonselective beta-blocker that blocks the action of catecholamines (adrenaline and noradrenaline) at both beta-1 and beta-2 adrenergic receptors) to be used safely as renin inhibitor , red blood cell invasion inhibitor, cardiovascular complication mitigator , and anticatabolizer in management of complicated COVID-19 infected patients with positive clinical outcomes.

Keywords: COVID-19, propranolol, RBC invasion inhibitor, anticatabolizer, cardiovascular complication mitigator, renin inhibitor

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus COVID-19. Common symptoms include fever, cough, and shortness of breath. Other symptoms may include fatigue, muscle pain, diarrhea, sore throat, loss of smell, and abdominal pain. The time from exposure to onset of symptoms is typically around five days but may range from two to fourteen days. As of 16 April 2020, more than 2.13 million cases have been reported across 210 countries and territories, resulting in more than 142,000 deaths. More than 540,000 people have recovered. (Zheng *et al.*, 2020) The standard method of diagnosis is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. Chest CT imaging may also be helpful for diagnosis in individuals where there is a high suspicion of infection based on symptoms and risk factors; however, it is not recommended for routine screening. (Li & Xia, 2020)

Coronaviruses are single-stranded RNA viruses, about 120 nanometers in diameter. They are spike glycoprotein which have 2 subunits S1 and S2. S1 binds to the cell receptor, on the other hand S2 fuses with the cell membrane. A host transmembrane serin protease TMPRSS2 facilitates the entry of SARS-Cov into the cells by two separate pathways. After the Spike S1 binds on the membrane surface of the cell, the

TMPRSS2 turns on the Spike and the ACE-2 turns off. The Spike binds with ACE-2. TMPRSS2 also acts on the S2 subunit of the spoken glycoprotein, which induces, activates, and facilitates the fusion of the virus into the cell membrane, irreversible conformational changes. (Wang *et al*., 2008) ACE 2 will be bounded, so this will decrease it is ratio inside the infected body by SARS-CoV , which lead to increase the occurrence of infection. Angiotensin causes non-transferrin-bound iron uptake by AT-1 receptor activation, leading to EC oxidative functional impairment. Overexpression of human ACE2 enhanced disease severity in a mouse model of SARS-CoV infection, demonstrating that viral entry into cells is a critical step. injecting SARS-CoV spike into mice worsened lung injury. Critically, this injury was attenuated by blocking the renin-angiotensin pathway and depended on ACE2 expression. Thus, for SARS-CoV pathogenesis, ACE2 is not only the entry receptor of the virus but also protects from lung injury. COVID-19 became highly lethal because the virus deregulates a lung protective pathway.

Propranolol as β1 antagonist decreases the contractility of blood vessels and arrhythmia. As β2 antagonist it can work as anti-catabolic for malnutrition inflammatory complex syndrome and it can reduce of hypokalemia in hyperthyroidism patients. Propranolol is the drug of choice as a prophylaxis for the risks of both primary and recurrent gastrointestinal hemorrhage in hepatic cirrhosis patient. It is used to treat number of types of irregular heart rate, thyrotoxicosis, capillary hemangiomas, performance anxiety, and essential tremors. It is used to prevent migraine headaches, and to prevent further heart problems in those with angina or previous heart attacks. (Chadda *et al*., 1986) .It's an acceptable drug for patients because it doesn't produce postural or exercise hypotension. It usually produces the best control of the supine blood pressure. (Cheng *et al*.,

2003). Propranolol, by its' β2 blocking reduces the hypermetabolic response. (Oberbeck & Kobbe, 2009).The non-selectivity of this drug would help us by making an advantage from each mechanism. Especially, we know that there are many correlations between Propranolol mechanism of action and COVID-19 infection pathology.

At this review we will discuss the positive outcomes of using propranolol as renin inhibitor, red blood cell invasion inhibitor, cardiovascular complications mitigator, and anti-catabolizer in management of complicated covid-19 infection depending on the pathology and the published clinical trials.

DISCUSSION

Renin-Angiotensin-Aldosterone system is cascade of physiologic events to regulate blood pressure. If the blood pressure decreases, blood flow to the kidney decreases and Renin which is pyrolytic enzyme that breaks down Angiotensin (liver enzyme) that catalyst Angiotensin-1. When Angiotensin-1 reaches the lung, it is converted into angiotensin II by an enzyme called Angiotensin-converting enzyme, or ACE for short. So angiotensin II binds to receptors in vascular smooth muscle and causes them to constrict, which increases the blood pressure. Finally, angiotensin II also stimulates the release of aldosterone by the adrenal glands. Aldosterone increases reabsorption of sodium in the kidneys which also increases water reabsorption. This results in increased blood volume, which also increases blood pressure. A simplified version of the pharmacology of the renin–angiotensin system is shown in the diagram below.(Aronson & Ferner, 2020).
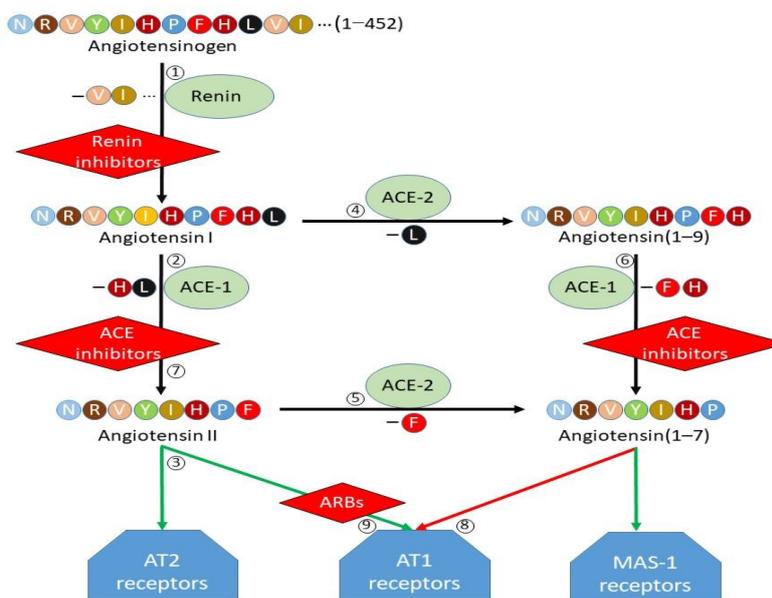
Experimental studies have suggested that angiotensin-2 (Ang 2) promotes iron (Fe) deposition in several tissues in lysosomal/endosomal structures in vascular cells. Ang 2 stimulate NADPH oxidase to promote superoxides in ECs, and Fe loading in the cells may generate active oxidant (hydroxyl radical) which lead to cell injury and dysfunction. (Aronson & Ferner, 2020) According to the diagram if we inhibit ACE-1 then Ang-2 level decreases, and indirectly increases the level of ACE-2, so that will lessen the risk of infection. Ang-2 normally binds at AT2 or AT1 receptors, ARBs prevent Ang-2 binding this will decrease the generation of it. Endothelial injury and alveolar epithelial damage from proinflammatory cascade are major pathophysiologic mechanisms in the early phase of ARDS, leading to the process of proliferation and fibrosis. Inflammatory biomarkers are founded in ARDS pathogenesis such as tumor necrosis factor alpha, interleukin 6, platelet activating factor. In the advanced stage, activated alveolar fibrocytes, fibroblasts and myofibroblasts may promote fibroproliferation. These inflammatory cytokines and increased pulmonary fibrosis may lead to higher mortality rate. The anti-inflammatory therapy or prevention of pulmonary fibrosis in ARDS may improve survival. Angiotensin II via activating nuclear factor-κB in monocytes makes proinflammatory responses. Nuclear factor-sec B activation and lipopolysaccharide-recruitment induced lung neutrophil is reduced by the inhibitor of the renin-angiotensin system ACEs or ARBs.(Kim *et al*., 2017) Propranolol is a potent lysosomotropic agent because of the presence of the ethanolamine side chain and its lipophilicity (Cramb 1986). COVID-19 binds with ACE2 receptors in the lung and enters the cells. Propranolol is an inhibitor of renin. (Saruta *et al*., 1980) From this point Propranolol would be a COVID-19 invasion inhibitor.

Erythrocytes are strongly implicated in the pathophysiology of Covid-19. The role of erythrocytes in the pathophysiology of Covid-19 is under-estimated; the co-efficient of variation of red blood cell distribution width (RDW) is predictive of severity of disease state. Elevated RDW is correlated with reduced erythrocyte turnover; red blood cells become smaller as they age and the delay in clearance expands the low-volume tail of the volume distribution. Suppressed erythrocyte turnover may indicate erythropoietin distress and function as a compensatory mechanism to maintain circulating red blood cell levels. Excess porphyrins in red blood cells can precipitate cell lysis and development of hemolytic anemia. Erythropoiesis and rapid hemoglobin turnover, Elevated serum ferritin levels are typical of acute porphyria and would be expected upon dissociation of iron from heme . (Mehta *et al*., 2020) A mechanism by which covid-19 might attack the 1beta chain of hemoglobin has been proposed; the product of open reading frame 8 (ORF8) binds to the porphyrin of heme and displaces iron, according to bioinformatics prediction analyses. The oxygen-carrying capacity of erythrocytes would therefore be compromised by COVID-19, thereby exacerbating the difficulties already experienced by the patient, in terms of maintaining partial pressure of oxygen in the alveoli (PaO2). (Europe PMC, 2019) Antimalarial agent depends on prevention g of Plasmodium falciparum invasion, Propranolol has been used in malaria for the same outcome. (Shahabi *et al*., 2014). By that it protects cells from RBCs invasion. Propranolol can do this prevention by its' effect on RBCs membrane. The interaction of propranolol with erythrocyte membranes at concentrations stabilizing intact erythrocytes against hypotonic hemolysis produced corresponding perturbations in membrane protein and particularly membrane phospholipid components as monitored by increases in the reactivity of membrane amino and sulfhydryl groups towards trinitrobenzenesulfonic acid and 5,5'-dithio-bis(2-nitro-benzoic acid), respectively. Membrane-propranolol interactions were also analyzed in terms of alterations produced in the kinetic properties of membrane enzymes. These experiments provided evidence that propranolol-induced perturbations were sufficiently generalized as to influence the activity of enzymatic processes associated with both inner and outer membrane surfaces. Configurational changes in membrane phospholipids were implicated in these effects of propranolol, which included alterations in functionally significant membrane-cation interactions, it is suggested that the findings described here may provide a basis for understanding molecular aspects of membrane stabilization in other systems. (Godin *et al*., 1976).

The effect of propranolol on the heart and blood viscosity which markedly increase in COVID-19 patient, Because of liberation of oxygen and Iron overload. Nonfunctional hemoglobin will produce more RBCs which lead to high blood viscosity. The effect of propranolol treatment was investigated in the myocardial ischemia-induced hyper viscosity state in anesthetized dogs. In untreated control dogs, low shear blood viscosity rose progressively, following an acute occlusion of the left anterior descending coronary artery; this effect was partially but significantly reduced by intravenously administered propranolol (0.2 mg/kg). The effect of the in vitro addition of propranolol was also determined upon viscosity of blood samples obtained at hourly intervals from dogs subjected to similar coronary ligation. The in vitro addition of propranolol did not produce a similar reversal of the hyper viscosity state observed in the blood obtained from dogs after coronary ligation. (Biro & Beresford-Kroeger, 1984)That explains the role of propranolol in

COVID-19 patients as cardiovascular protector from further complications.

Infected patient may develop increase rate in catabolism which is degradative metabolism that promote the release of energy and leading to the breakage of complex materials (such as proteins or lipids). In order to prevent catabolism by protect muscle mass we suggest the use of beta blockers. Beta blockers rises circulating triglyceride and low-density lipoprotein, it acutely decreases metabolic rate and increase protein oxidation. (Lamnot, 1995) Propranolol decrease catecholamine activity and has direct effects on protein-flux machinery or could act indirectly by changing endogenous insulin responsiveness, cortisol activity, or regional blood flow. Propranolol decreases lean-mass catabolism in severely burned patients. These changes would presumably improve the patients' strength and ability to recuperate. This drug has a benefit for a wide variety of patients who may have a negative nitrogen balance, such as those with trauma and those who are undergoing general surgery. (Herndon *et al*., 2001)

Propranolol was patented in 1962 and approved for medical use in 1964. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system .It can be taken by mouth or by injection into a vein. The formulation that is taken by mouth comes in short-acting and long-acting versions. Propranolol appears in the blood after 30 minutes and has a maximum effect between 60 and 90 minutes when taken by mouth. (George *et al*., 1972) Common side effects of Propranolol include nausea, abdominal pain, and constipation. (Stephen, 1966).According to literature we can conclude that Propranolol has quadrable effects which will show positive clinical outcomes in COVID-19 infected patients.

CONCLUSION

The management of COVID-19 should be individually studied case by case depends on what symptoms the patients develop and other risk factors, considering the adverse drug reaction and drug-drug interaction. In summary, Propranolol may act as an interventional treatment in complicated COVID-19 infection by its quadruple positive clinical outcome (Renin inhibitor, anti-catabolizor, red blood cell invasion inhibitor and cardiovascular complication mitigator) propranolol is not expensive ,safe and Available in all countries make it the best choice to try in COVID-19 infected patients so We suggest a robust clinical trial to confirm effectiveness of it.

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