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Paradoxical role of oxygen in the treatment of patients with COVID-19

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Dear Editor,

Coronavirus disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was declared a pandemic by WHO on 11 March 2020 and has adversely affected human society and disrupted global health [1]. The single-stranded RNA virus belongs to the family Coronaviridae, which has at least 4 structural proteins including Nucleocapsid protein (N), Spike protein (S), Membrane glycoprotein (M), and the Envelope protein (E). The four structural proteins of the virus along with the help of the ACE-2 receptor of the host cell are known to be implicated in the pathogenesis of the disease and regulation of its severity. The disease may progress from a mild respiratory illness to acute respiratory distress syndrome (ARDS) and finally to death [1-3]. Oxygen therapy is one of the most commonly used treatment modalities used for the treatment of hypoxemic respiratory failure in COVID-19 patients. The concentration as well as flow of oxygen used for treatment to aid ventilation is directly proportional to disease severity [4]. In severe ARDS, fluid in the alveoli causes hypoxemia leading to fibrosis of the lung tissue which in turn results in increased pressure required to sustain breathing. In such situations to improve the oxygenation of blood and to therefore help reduce the work of breathing, physicians prefer the use of ventilators or hyperbaric oxygen therapy to support patients of ARDS especially during the stages of lung recovery [5]. However, on postmortem examination of lungs of COVID-19 patients affected with ARDS, features bearing semblance to hyperoxic lung injury such as presence of enlargement of alveolar spaces, capillary thrombosis, alveolar edema, alveolar hemorrhage, perivascular infiltrates, vascular remodeling, and scattered fibrosis were seen [4].

The World Health Organization (WHO) recommends oxygen therapy during resuscitation of COVID-19 patients but during the administration of this therapy, cases of death attributed to the toxicity of oxygen have been reported when oxygen saturation levels are maintained above 96% [5,6]. Hyperoxia causes the generation of reactive oxygen species (ROS) within the lungs wherein intracellular ROS originate as a result of one electron reduction of molecular O_2 to superoxide ion and even further reduction to form hydroxyl radical [7]. Furthermore, the continued production of ROS activates both apoptotic and necrotic pathways to cause epithelial cell death and production of decreased growth factors that result in cell death of the alveolar epithelium [8]. These factors contribute to progressive permeabilization of the alveolar-capillary membrane, allowing the escape of edema fluid and blood into the alveolar space leading to hypoxemic respiratory failure and death [8,9]. It is well known that ROS cause lung injury but moreover and hitherto we presently would like to draw your kind attention to the very recent findings that suggest that exposure to hyperoxia increases epithelial expression of a putative SARS-CoV-2 co-receptor in lungs of neonatal mice and human lung tissue [10]. This suggests that a high concentration of oxygen given as treatment for patients with COVID-19 may paradoxically increase the chance of getting infected.

With the existence of contradictive information in a plethora of clinical situations for the use of oxygen therapy in COVID-19, the need to understand and regulate the parameters of oxygen supply in such patients is a pressing priority. Presently there are a few challenges and limitations regarding appropriate oxygen administration and proper knowledge of the same among clinicians and other healthcare staff. In patients with co-existing conditions such as Chronic obstructive pulmonary disease (COPD), the depression of normal ventilation may be precipitated due to oxygen supplementation, as they primarily depend on the chronic hypoxic respi-

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ratory drive to breathe. The hypercapnic stimulus is lost on treatment with oxygen therapy resulting in hypoventilation in these patients [11,12]. Furthermore, giving only pure oxygen can result in absorption atelectasis, which is the collapse of the dependent part of the lungs due to oxygen being taken up too quickly by the alveoli [13]. Retinopathy of prematurity (ROP) is also a known complication particularly seen in low birth weight as well as very premature infants exposed to oxygen therapy. Therefore, it is recommended to maintain 50-80mm of Hg PaO_2 in infants requiring oxygen [14]. Another important factor to also be considered is the possible risk of bacterial contamination associated with oxygen therapy caused through use of particular humidification systems or nebulization devices [15].

However, a few possible solutions that can be considered to overcome the aforementioned risks and complications during treatment of COVID-19 with oxygen therapy are: i) Continuous or repeated regular monitoring of blood oxygen levels (SpO_2) can help prevent hyperoxia and its side effects; ii) It has been found that Hypoxia Inducible Factor 1 Subunit Alpha (HIF1-Alpha) levels decrease in cases of hyperoxic injury, therefore a serial measurement of its levels may help in diagnosis as well as prognosis of hyperoxia [16]; iii) Hyperbaric oxygenation therapy sessions with air breaks may be employed to prevent hyperoxia [16]; iv) The use of sterile and appropriate humidification or nebulization systems can aid in appropriate delivery of oxygen without contamination; v) Gradual steady increase in oxygen supply to patients with COPD and cautious use of oxygen therapy in preterm and low birth weight infants to prevent complications; and vi) Use of High Flow Nasal Therapy (HFNT) as it can help deliver exact and pre-determined amount of FiO_2 and generates a small positive end expiratory pressure effect, improving oxygenation, respiratory mechanics and end-expiratory lung volume, reducing the work of breathing and offering good comfort to the patient [17].

As there still exists some lacunae in information about the treatment of COVID-19 patients with oxygen, along with lack of robust guidelines we believe that further future research related to the questions mentioned below will most definitely provide insight that will aid clinicians in helping manage patients with COVID-19 effectively and thus leading to better treatment outcomes and reduced morbidity and mortality.

1. What is the appropriate mode, dosage, and timing of oxygen administration to aid in treatment by maintaining appropriate oxygen saturation whilst not causing any oxygen-related toxicity in COVID-19 patients?
2. What conditions or co-morbidities in patients with COVID-19 might necessitate an alteration in the amount of oxygen to be provided or reconsider an alternate mode of treatment?
3. Which additional drugs or therapies can be used to minimize or negate the complications arising from hyperoxia other than that of antioxidants?

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