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Editorial
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A Possibility of Using Mesenchymal Stem Cell Therapy in Combination with Hyperbaric Oxygen Therapy for Treating COVID-19 Patients

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Editorial

By the end of 2019, several pneumonia cases rooted in "unknown cause" were registered in Wuhan, Hubei Province, China. An investigation was initiated by the end of December itself by the Centers for Disease Control and Prevention, China (CDC equivalent of the US). However, it was not until January 30th, 2020, when the World Health Organization (WHO) recognized the it as a pandemic and declared the outbreak of 2019-nCoV coronavirus as a public health concern [1,2]. By the time of appearance of this report, it is very likely that more than 70 million cases and 1.5 million deaths could be recorded in the whole world.

According to phylogenetics studies, 2019-nCoV belongs to the subgenus *Sarbecovirus*, family *Coronaviridae*, and it was found to be closely related to two bat CoV strains (bat-SL-CoVZC45 and bat-SL-CoVZXC21). Interestingly, this new virus shares only 79.5% of its genetic information with SARS-CoV, and only approximately 50% with MERS-CoV. Hence, it is believed that the origin of 2019-nCoV is a bat CoV which started infecting humans after a zoonotic process, a process which takes place once in a while in situations not well understood [1-3].

The coronavirus has five structural proteins, including envelope membrane protein (small and large), spike, nucleoprotein, and hemagglutinin esterase and membrane protein. The S-protein is conformed of two functional subunits S1 and S2, which are responsible for interacting with Angiotensin Converting Enzyme 2 (ACE2) receptor, and thereby facilitating the viral entry into the host cells. Specifically, priming of the spike protein by TMPRSS2 (Transmembrane Proximal Serine Protease 2) a host protein is required to facilitate the entry of the virus in the host cells [4]. The high presence of ACE2 receptors on type I and type II alveolar epithelium of upper respiratory system, and endothelial cells of heart, kidney tubular epithelium, pancreas, endothelial cells and enterocytes, besides affecting the respiratory system, 2019-nCoV is reported to trigger a systemic pathology and causes multiple organ failure as the infection activates a strong inflammatory response [5], resulting in a cytokine storm causing abnormally increased levels of C-Reactive Protein (CRP), higher White Blood Cell Count (WBC), higher neutrophil count, lower lymphocyte count, among others. These factors complicate the recovery process in severe cases of COVID-19 [6,7]. Recent studies report development of coagulopathy also in patients infected with 2019-nCoV virus. It has been characterized as increased D-dimer and fibrinogen or fibrin degradation products, as well as abnormalities of prothrombin time, acute partial thromboplastin time, and platelet counts. Though the exact mechanism of this pathology is still under investigation, evidence suggests the observed coagulopathy is associated with endotheliopathy that causes thrombotic microangiopathy result in microcirculatory impairment which is consistent with the finding of microcirculatory clot formation and endothelial apoptosis in the post-mortem repots of COVID-19 patients. These findings could explain the sudden cerebrovascular complications like myocardial ischemia, and thromboembolic complications, seizures, and strokes reported in these patients [8-11].

Several treatments have been proposed to treat the complications caused by the viral infection. Although none of them has proven to be 100% efficient, the use of Stem Cell Therapy has gained confidence recently. Mesenchymal Stem Cells (MSCs) are known to have a great immunomodulatory, anti-inflammatory, anti-fibrotic, anti-apoptosis and angiogenic properties *in vivo* [12,13]. Furthermore, infusion of MSCs has proven to be safe in treating several indications like neurodegenerative conditions, autoimmune diseases, systemic maladies, and respiratory disorders [14]. Transplantation of ACE2- MSC significantly improved the functional outcome in

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seven patients infected with 2019-nCoV, in Beijing, China [15]. Many studies have demonstrated that the use of MSC therapy had successful outcomes in patients infected with SARS-Co-19, and therefore it is a viable therapeutic option. While the immunomodulatory properties of stem cells could regulate the cytokine storm and prevent multiple organ failure, the tissue regeneration properties might help the organs to regain their normal functions [15-17]. The US-FDA has approved many clinical trials (https://clinicaltrials.gov/ct2/show/NCT04444271) for using the MSCs infusion therapy which are undergoing, and the results are yet to be published.

In pursuit of an effective means for regulating the cytokine storm, administration of Hyperbaric Oxygen (HBO_2) therapy also has been performed in some clinical trials. The underlying theory proposes that availability of higher than normal level of oxygen during HBO_2 therapy can safely reduce the inflammatory response by attenuation of the innate immune system, increase hypoxia tolerance, and thereby can prevent multiple organ failure [18]. In a clinical trial, two critically ill patients infected with 2019-nCoV showed significant improvements in their condition after being treated with HBO_2 therapy. The therapy resulted in elevation in the blood oxygen saturation levels which may reduce lung inflammation caused by the viral infection. Also, dyspnea and shortness of breath were immediately alleviated after the first treatment itself [19]. Furthermore, in another report, five patients presenting with significantly low oxygen saturation levels showed excellent outcomes after receiving mg HBO_2 therapy [20]. This therapy proved to be safe and lowered or eliminated a need for mechanical ventilation [20]. Many clinical trials for using HBO_2 therapy are also approved by the US-FDA, and are under process (https://clinicaltrials.gov/ct2/show/NCT04332081).

Since the two therapeutic options in discussion use two fairly independent modes of action, a natural question originates whether these two can be used in combination. Both of the therapeutic interventions, administration of MSCs and HBO_2 therapy have been proven to be efficient and safe in treating patients infected with COVID-19 in preliminary clinical trials. There is a strong probability that the immunomodulatory properties of the MSCs could become more potent in down regulating of the strong response of the immune system following the infection when used in combination with the HBO_2 therapy on one hand. On the other hand, the regeneration of organs accelerated by the angiogenesis promoting properties recorded in MSCs [17,18] could be further potentiated by higher levels of oxygen incurred by the HBO_2 therapy. These findings strongly indicate that the administration of MSCs in combination with HBO_2 therapy in patients infected with 2019-nCoV has the potential for a still better outcome leading to efficient recovery. Also, there is a great possibility that the combination therapy may lower down the need of mechanical ventilation significantly because of HBO_2 therapy generated higher oxygen availability in different tissues, and immunomodulatory and angiogenic activities of the MSCs.

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