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The use of negative oxygen ion clusters [$O_2^-(H_2O)_n$] and bicarbonate ions [HCO_3^-] as the supportive treatment of COVID-19 infections: A possibility

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ABSTRACT

The COVID-19 or novel coronavirus SARS-CoV-2 pandemic is challenging worldwide healthcare system and severely affecting global economy. Furious efforts to end the pandemic including prevention of spread of SARS-CoV-2, use of antiviral drugs, symptomatic treatments and vaccination are underway. But there are no effective treatments available to save the dying patient in stage 2 (pulmonary) and stage 3 (hyperinflammation) of the infection. The detailed genetic and phenotypical analysis of SARS-CoV-2 revealed that the spike protein (S1) has increased positive charges (compared to SARS-CoV) on them and are responsible for attachment to human angiotensin-converting enzyme 2 (ACE2) receptor and infection by the virus. In addition, it was also reported that the inflammation in the tissue rendered the lung environment more acidic supporting the fusion of SARS-CoV-2 with the cells. We hypothesize that the intermittent use of the oxygen ionizer generating negative oxygen ion clusters [$O_2^-(H_2O)_n$] and sodium bicarbonate nebulizer (generating HCO_3^-); when connected to ventilator inlet or oxygen concentrator will neutralize the spike protein of the virus in respiratory tract and lungs and change the lung environment to neutral/alkaline condition respectively facilitating improved oxygen pressure in blood. These physical changes can effectively reduce the viral burden and help the patient recover from the infection faster.

Introduction

Till date around 185 million infections and 4 million deaths were reported globally due to coronavirus disease (COVID-19). This virus is also known as SARS-CoV-2 and mainly attacks the respiratory system and lungs in humans, ultimately leading to pneumonia like condition and death. This viral infection was originated in Wuhan, China and spread through out the world in first quarter of the year 2020 [1]. Initially in first wave, this virus mainly infected elderly patients (above the age of 50) and proved deadly for the patients with pre-existing medical conditions (diabetes, blood pressure, lung diseases etc.) [2]. In second wave of infection all adult aged population has suffered, specifically in countries like Brazil, and India. Now at the brink of the third wave, more lethal mutated strains of virus are threatening the world. It is observed that the new viral strain is infecting younger population too [3]. This is the alarming situation for the whole world as the vaccination program is still in its intermediate stage and there is no medication available for the treatment of the COVID-19 infections. The questions are also raised against the effectiveness of the available vaccine against the newly mutated viral strains.

The coronavirus disease (COVID-19) progress mainly in 3 stages, Mild stage [with non or mild pneumonia conditions, most commonly occurring (almost 80%) cases], Severe/pulmonary stage [dyspnea, increased respiratory frequency and reduced blood oxygen level fluctuating from 60 to 90% occurring in almost 15% of cases] and Critical/hyperinflammation stage [characterized with respiratory failure, multiple organ dysfunction/failure (MOD/MOF) and septic shock occurring in 5% of cases] [4].

The symptoms observed in the Mild stage of the infection are fever, dry cough, tiredness, loss of taste or smell, aches and pains, sore throat, headache, a rash on skin and diarrhoea. The more serious symptoms indicating Severe/pulmonary stage are difficulty breathing/shortness of breath, chest pain and loss of speech or movement. The Critical/hyperinflammation stage is marked with sever shortness of breath, sever chest pain, dangerously low oxygen levels in body and complete loss of lung movements requiring intervention of life support instrument like ventilators to assist breathing and maintaining oxygen in blood. Generally, the Mild stage symptoms are misunderstood as Flu or

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Influenza symptoms and the COVID-19 patients become carrier of the virus and can infect other people [5].

There are no proven antiviral treatments available against COVID-19 virus however use of antiviral Ramdisavier, chloroquine and corticosteroid Dexamethasone if used in proper stage of infection can help to reduce supportive oxygen and ventilation time in Severe/pulmonary stage and Critical/hyperinflammation stage [6]. As preventive measures, use of N95 masks, social distancing, frequent hand washing, sanitization of the places, lockdowns and vaccination were employed and were found effective controlling the spread of infection [7,8].

The present condition of the COVID-19 infection and scarcity of the treatment options and resources is alarming and leading to increasing deaths around the globe. The oxygen therapy was effective in stage 2 (pulmonary) and moderately effective in stage 3 (hyperinflammation) of the COVID-19 infection. There is a need of effective supportive therapy to oxygen therapy; thus, in this hypothesis article, the use of negative oxygen ion clusters $[O_2^-(H_2O)_n]$ and bicarbonate ions (HCO_3^-) as the supportive treatment for COVID-19 infections is proposed.

Hypothesis

It is hypothesized that the negative oxygen ion clusters $[O_2^-(H_2O)_n]$, when supplied through ventilator or oxygen concentrator intermittently, will neutralize high positive (+) charges present on the spike protein of the COVID-19 virus. Similarly, the HCO_3^- ions supplied intermittently through ventilator or oxygen concentrator along with $O_2^-(H_2O)_n$ clusters as nebulized sodium bicarbonate will change the acidic bronchial environment to neutral/alkaline conditions leading to enhanced CO_2 exhale and effective maintenance of oxygen pressure in blood and faster recovery of the patient.

Evolution of hypothesis

The charges on spike protein

The SARS-CoV-2 spike (S) protein is a transmembrane glycoprotein (180–200 kDa) with 1273 amino acids and has two subunits (S1 and S2) playing multifaceted role in COVID infections. The S1 subunit (14–685 residues) is responsible for host cell receptor binding and S2 subunit (686–1273 residues) is responsible for fusion of the viral and cellular membranes. The S1 is a signal peptide containing N-terminal domain with 14–305 residues and receptor-binding domain (RBD) with 319–541 residues. S2 has the fusion peptide (FP) with 788–806 residues, heptapeptide repeat sequence 1 (HR1) with 912–984 residues, HR2 with 1163–1213 residues, trans membrane (TM) domain with 1213–1237 residues, and cytoplasm domain with 1237–1273 residues. The S1 subunit with receptor-binding domain (RBD) has ten more positively charged amino acid residues (Arg346, Arg357, Arg403, Lys417, Lys444, Lys458, Lys462, His519, Lys529 and Lys537) compared to SARS-CoV S RBD that increased the overall positive charge of the S1 RBD in COVID-19 virus [9–11]. The S glycoprotein has 22 predicted N-linked glycosylation and three O-glycosylation sites. The mutations of the virus regularly modify the glycan in the S glycoprotein and fool the host immune system and increase the infections many folds. Thus the combination of increased positive charges on the S glycoprotein and complex glycosylation enhanced the SARS-CoV-2 - ACE2 receptor binding by10 to 20 fold higher compared to SARS-CoV [12–14].

The genetic mapping studies of COVID-19 or novel coronavirus SARS-CoV-2 reveled that though SARS CoV-2 is a betacoronavirus closely linked to the SARS-CoV (77% identical sequence); the spike protein charges differ largely in both. The SARS-CoV-2 spike glycoprotein bares ten more positively charged amino acid residues that have increased the affinity of the spike glycoprotein to negatively charged binding regions of ACE2 receptors rendering the SARS-CoV-2 virus more infectious compared to other SARS strains [15–19] (Fig. 1a). Thus, one of prime site of viral infection i.e. SARS-CoV-2 virus - ACE2 receptors

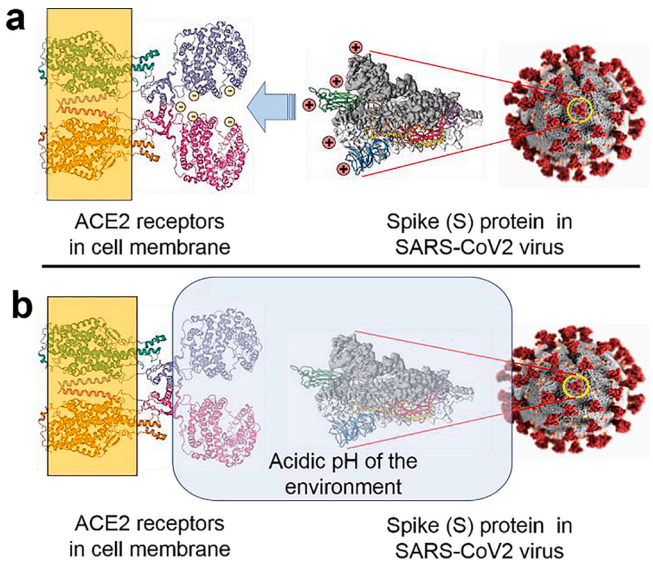

Fig. 1. a. The improved electrostatic interaction of the S – protein from SARS-CoV-2 virus and ACE2 receptors of the lung cells due to increased numbers of positively charged amino acid residues in the S1 – protein; b. The acidic environment helping in favorable configurational changes in S – protein as well as ACE2 receptors leading to attachment and fusion of virus and cells.

binding, suggested an important role of electrostatic bonding and alterations in glycolylation. These binding forces also form the basis for successful (good antigenicity) vaccine development [20,21] and virus-cell fusion inhibitor (lipopeptides, aptamer and carbon nanoparticles) development [22–24].

The pH of diseased bronchoalveolar fluids

It is reported that the pH of the bronchoalveolar fluids of a COVID-19 patient is acidic (resulting in respiratory acidosis with pH < 7.30) [25–27]. It was reported that the acidic pH favors the binding of the S – protein with ACE2 receptors and ultimately fusion of the viral protein coat resulting in lungs as well as systemic infection [28–31] (Fig. 1b). The respiratory acidosis begins with COVID-19 infection of lungs ultimately resulting in pneumonia conditions and little or no gaseous exchange through lungs. This leads to increase in CO_2 concentrations in blood causing systemic acidosis. As the infection conditions worsen, the pH further decreases resulting in acute shortage of the oxygen (average $pCO_2 > 40$ mmHg and average $pO_2 < 35$ mmHg) [32]. Thus, more the lung infection more is the respiratory acidosis, more the acidosis more is the pCO_2 levels and less pO_2 levels in blood; as the O_2 is very less in body, many organs slowly stop functioning normally [33,34].

In addition to acidic pH, COVID-19 infections also result in airway inflammation leading to cytokine storm, mucus hypersecretion and build-up. The formation of mucus plugs cause airway obstruction and respiratory failure. Deaths due to mucoid tracheitis and acute respiratory distress syndrome (ARDS) were observed in 33 % of COVID-19 patients [35]. In addition to this, ARDS also enhanced secretory phospholipase A2 (sPLA2) activity degrading the phospholipids in the lungs which are the major component of surfactants present in respiratory system. These surfactants reduce the surface tension of the mucus and help to reduce fluid infiltration into the alveoli. Dysfunctioning of surfactant also changes alveolar capillary shape and also alters the pulmonary blood flow to exacerbate hypoxemia. Thus it is necessary to provide the supportive treatment which can help in the maintenance of the surface tension of the mucus to improve the recovery of the COVID-19 patient [36].

The ionized oxygen

The health advantages of ionized air were explored and exploited for last few decades. The ionized air effectively prevented the airborne transmission of influenza virus [37]. Specifically, in recent years, the health benefits of negative air ions (NAIs) are being studied. The electrically charged molecules or atoms can be generated naturally by the shearing forces of water (Lenard Effect), natural and artificial corona discharge (thunderstorms and lightning), sunlight (ultraviolet), radiant or cosmic rays, pulse electric stimulation and by plants. The half-life of these NAIs is short (from few seconds to 100 s) and depends on the source of the NAI generation. NAIs available as water clusters has comparatively longer half-life $[O_2^-(H_2O)_n \geq 60$ s). These NAIs benefit health by significantly reducing the level of serotonin in blood and/or brain, activation of natural killer (NK) cell and by attaching themselves to particles such as dust, mold spores, allergens, viruses and neutralizing them. NAIs were also reported to show beneficiary effects on cardiovascular and respiratory system as well as on mental health [38]. These NAIs are very effective (97% viral deactivation in 45 min) against aerosolized viruses [39] (Fig. 2a). The NAIs, specifically negative oxygen ions are very effective in reacting with lipids, proteins, glycoproteins, carbohydrates, and nucleic acids of the viruses and neutralizing them in spite of mutations [40]. The *in-vitro* effectiveness of NAIs on airborn, aerosolized and suspended virus inactivation and other health benefits were already proven. Thus, negative oxygen ions cluster is expected to effectively neutralize multiple existing and newly emerging *SARS-CoV-2* variants as proposed in the hypothesis.

The bronchoalveolar pH change

The studies were conducted to analyze the SARS-CoV-2 virus binding and fusion inhibition to the ACE2 receptors and ultimately to the bronchoalveolar cells in the presence of raised pH of the bronchoalveolar fluids. It was clearly observed that with the change (increased) in pH of the bronchoalveolar fluid, the viscosity of the fluid and mucus was reduced and can be easily taken out (Fig. 2b). Most of the COVID-19 patients with reduced oxygen saturation of around 50 % were recovered within a week. The pH of the bronchoalveolar fluid can be effectively raised using a ventilator or oxygen concentrator delivered

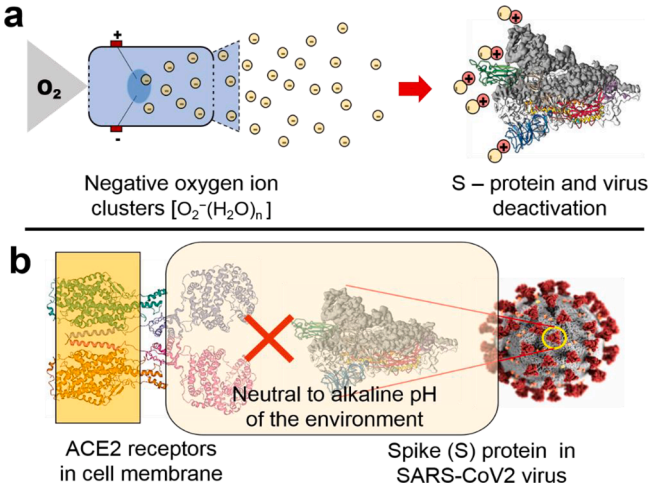

Fig. 2. a. The negative oxygen ion clusters generated by ionizer and supplied by ventilator/oxygen concentrator, might interact with the positively charged S1 – protein amino acid surface residues and might deactivate the whole S – protein; b. The change in the bronchoalveolar fluid pH to neutral or alkaline conditions with nebulized sodium bicarbonate (NSB) will change the viscosity of the fluid, allow better gas exchange in lungs and do not allow the favorable conformational change of the S - protein and ACE2 receptor avoiding virus attachment and fusion.

nebulized sodium bicarbonate (NSB). NSB is being routinely used in cystic fibrosis (CF) patients and in chloride inhalation toxicity but recent studies showed promising results of faster recovery from Stage 2 of COVID-19 infection and thus proposed in this hypothesis as a combination therapy with negative oxygen ion cluster $[O_2^-(H_2O)_n]$ therapy [41,42]. NSB is will also support in the maintainse of the pH in respiratory system by improving the surfactant activity. Thus reduced surface tension of the mucus helps in easy expulsion of the mucus from the lungs. The pH change and mucus clearance will also improve pulmonary blood flow ultimately leading to faster recovery of the COVID-19 patient [43,44].

The hypothesized supportive treatment

The COVID-19 patient might needs medical oxygen at 60 *l*/minute (86,000 *l*/day) or concentrated oxygen (85–95% at 5–10 *l/minute*) as supportive therapy to fight reduced pO_2 levels in blood. It is proposed that the medical oxygen (O_2) or concentrated oxygen (generated in oxygen concentrator) can be intermittently (for 45 min every 3 h) ionized and converted to negative oxygen ion (O_2^-). This O_2^- can be passed through humidifier to form a negative oxygen ion cluster $[O_2^-(H_2O)_n]$ and will be delivered to patient (through ventilator or mask). At the same time, intermittently (5–10 ml every 6 h) nebulized sodium bicarbonate (NSB) therapy with 3.5–5% concentration (4.2% reported for some COVID-19 patients) can be delivered through the same inspiratory limb of the ventilator tubing or by connecting to the nebulizer mask of oxygen concentrator tubing. Ventilator can be set on positive expiratory pressure (PEEP) of 15 so as to maintain proper ion cluster flow as well as NSB in lungs [45,46] (Fig. 3a).

In general, it is proposed that the negative oxygen ion cluster $[O_2^-(H_2O)_n]$ after reaching bronchoalveolar spaces will neutralize the surface positive charges of S – protein and might denature it. Thus, it will avoid binding and fusion of virus with ACE2 receptors of the bronchial cells. The NSB supplied will change the pH of the bronchoalveolar fluids and mucus. This will enhance the liquefaction of the fluids and mucus as well as enhance the gaseous exchange in the lungs. As the gaseous exchange in lungs will improve, it will improve pO_2 in blood and reduce the respiratory acidosis. The negative oxygen ion cluster $[O_2^-(H_2O)_n]$ will additionally support the oxygen pressure stabilization and other the health benefits ultimately leading to faster recovery of the COVID-19 patient.

The use of negative oxygen ion cluster and NSB therapy can provide

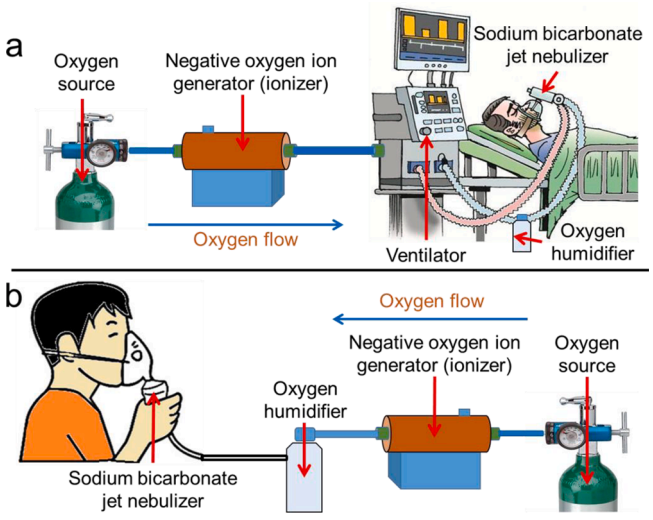

Fig. 3. The hypothesized supportive treatment for a. stage 2 and 3 ventilator assisted patients; b. primary stage showing possibility of progression in to stage 2.

maximum benefit to stage 2 patients where the lungs are not very badly affected. The negative oxygen ion clusters will neutralize the positively charged SARS-COV-2 S1 RBD further inhibiting the infection and spread of virus in lung tissue and provide most needed oxygen in lungs to maintain pO_2. The NSB therapy will enhance the pH of the lung, disturbing the ecology of the infecting virus as well as reestablishing surfactant actions helping in reduction of viscosity and easy expelling of the mucus. In addition, NSB will also facilitate the gas exchange in the lungs reducing systemic acidosis and maintaining pO_2.

In the case of stage 3, where the damage to the lung tissue is severe, the negative oxygen ion clusters can help to reduce the viral burden in the bronchial fluids and provide pure oxygen. At the same time the NSB therapy will help to change the pH and reduce the viscosity of bronchial fluid and mucus, so that it can be easily taken out of lungs. But, the response and recovery of the patient due the treatment of the negative oxygen ion clusters and NSB will be limited. The limitations will be due to systemic (multi organ) infection of the virus, major loss in the breathing/lung capacity and severe decrease in blood pO_2.

It is also proposed that, all the benefits of negative oxygen ion cluster $[O_2^-(H_2O)_n]$ as well as NSB can also be used in mild cases (showing possibility of progression in to stage 2) by supplying the negative oxygen ion cluster $[O_2^-(H_2O)_n]$ through pneumatic jet nebulizer containing NSB solution to the patient (Fig. 3b).

Conclusion

In the middle of the second wave of the COVID-19 pandemic the death rate was very high, specifically in countries like India and Brazil. All healthcare systems in these countries and around the world are struggling to control and minimize these death rates. There are no fixed medications and treatments available to completely cure COVID-19 infections. The stage 2 and 3 patients only has ventilated oxygen as a desperate supportive treatment. In this hypothesis, a modified oxygen supportive therapy along with nebulized sodium bicarbonate (NSB) therapy is proposed. This modified supportive therapy will combine the advantages of ventilated/concentrated oxygen, negative oxygen ion cluster and pH change in bronchoalveolar fluid and space. With this supportive therapy, SARS-CoV-2 virus inactivation due to negative oxygen ion, liquefaction of the bronchoalveolar fluids due to pH change, inhibition of the SARS-CoV-2 virus – lung/respiratory tract cells binding and fusion, better gas exchange in lungs to enhance blood oxygen levels and faster recovery of the COVID-19 patients is expected. In the brink of the third wave, more lethal mutated strains of virus (Kent variant, Delta and Delta plus variants) are threatening the world. The proposed role of negative oxygen ion cluster $[O_2^-(H_2O)_n]$ and NSB supportive therapy can effectively help to fight the infection from these new strains due to its non-specific and physicochemical nature.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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