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Silent Hypoxia: Outcome in COVID-19

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ABSTRACT

The coronavirus 2019 disease which has originated from the virus named severe acute respiratory syndrome also known as SARS-CoV-2. This disease was first come to knowledge from Wuhan, a city in China during late December. And has turned out to be a universal pandemic in the month of March 2020 as said by the organisation WHO. It is noted that the population who were affected by this virus are 2.6 million including 210 countries till 22nd April 2020 and the count still continues.
COVID-19 or corona virus disease has caused a massive death number across the globe. It has mainly affected the respiratory system. Whereas it has also caused various complication to other organs as thromboembolic problems, myocardial ischemia. The exact mechanism behind this still unknown. It presents with lack of dyspnea and extremely low oxygen saturation level, which makes them exceptionally at higher risk. It could happen that coronavirus has a distinctive action on receptors involved in chemo sensitivity to oxygen, but well-established pathophysiological mechanisms can account for most, if not all, cases of silent hypoxemia. These mechanisms consist the way dyspnea and the respiratory centres reacts to low levels of oxygen, the way the Prevailing Carbon Dioxide tension ($PaCO_2$) alters the brain's response to hypoxia, effects of disease and age on control of breathing, inaccuracy of pulse oximetry at low oxygen saturations, and temperature induced shifts in the oxygen dissociation curve. Oxygen saturation reading and lack of dyspnea are some factors which are alarming to physicians along with its outcome on the respiratory centres.

Key words: COVID-19, Hypoxia, Dyspnea, Control of breathing, Hypoxemia, Oxygen dissociation curve

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INTRODUCTION

When we look into the case of acute lung disease caused by novel coronavirus then we came across with patients who have developed acute respiratory distress syndrome. In this case, the respiratory centre in the brain is stimulated due to the increased concentration of CO_2 due to various causes (low level of oxygen in blood, metabolic acidosis, lung and chest wall receptors get activated etc.). This all will result into a condition of increased level of carbon dioxide in blood. We can observe that in cases of corona virus disease patients having pneumonia if confirmed with the conditions of the acute respiratory distress syndrome shown to have normal respiratory compliance and vasculopathy which are said to be the reason behind the hypoxemia. Considering above scenario, difficulty in breathing and alveolar damage due to fluid accumulation may be least because in elderly and diabetic patients this is a not a strong signal of the respiratory centre. Also low concentration of partial pressure of CO_2 ends up in low hypoxic condition.

LITERATURE REVIEW

Corona virus has a major effect on the central nervous system by two ways:

- Directly by neurons and blood and
- Other route.

Something came to our knowledge that corona virus causes nerve cell destruction and disturbs the equilibrium of neuropeptides which is responsible for cellular outcome. Therefore, corona virus involved in nerve cell destruction that may controls the breathing process. When the arterial oxygen partial pressure is below 80 mm hg and when it gets severe with value below 60 mm hg is called as Hypoxemia [1]. This condition is related to the clinical features of distress which are as follow rapid breathing and difficulty in breathing. Whereas, there were also some patient who weren't developing these features of low level of oxygen. The method to detect this condition is by using oxygen saturation probe and calculating arterial blood gas. The above situation is what termed as happy hypoxaemia [2,3]. If this situation missed to be diagnosed at early stage then will land up into conditions like cytokine storm and severe hypoxia.

Factors responsible for silent hypoxia

- Angiotensin converting enzyme overexprssion
- Damage to endothelium by Nf-KB
- Cytokine storm
- Secondary infections by corona virus affecting brains, kidneys

How does hypoxaemia occurs in COVID-19

The corona virus has resulted into inflammatory outcome which has ranged from low to very high in severity along with the evidence of diffuse alveolar damage in the lungs. When the document of patients with corona virus was evaluated then what was found is mild to moderate mononuclear responses seen which comprised of remarkable collection of CD4+ cells throughout the small arteries that had gone under thrombosis and there were some foci of haemorrhages along with it. Pulmonary microvascular thrombosis is what, is confined to the lungs but can result into an further process that happens in the most adverse kind of this viral disease [4,5].

Low level of oxygen in blood in corona virus patients showing the lung injury which is diffuse in nature. It could be consisting to 3 different types. Because of the increased factors that is ventilation-perfusion mismatch (V/Q defects) in the injured lung, its main types in patients are as follows hypoxic and hypercapnic respiratory failure [6,7]. These two types are the second category of hypoxemia that occurs infrequently among COVID-19 patients. Although hypercapnia results to breathlessness in normal individuals, some COVID-19 patient's do not complains of dyspnea even with the development of severe hypoxemia [8]. The third kind of hypoxemia is pure hypoventilation and is marked by hypoxemia in the condition of a normal arteriovenous oxygen gradient, which is unusual among these patients [9,10].

When there is inflammatory reaction in the activation of stretch receptors of the lungs, there is destruction of the epithelium of the alveoli and lung parenchyma. The signals which are generated in this due course are transferred to brain in form of afferents signals and its further processing done specifically in the (hippocampus, amygdala and hypothalamus) plus cortex region which controls the sensorimotor functions [11,12]. This condition has been reported to be related with detection of difficulty in breathing [13].

When the calculation was done of partial pressure of carbon dioxide and power of hydrogen ion in the brain is needed then the central respiratory chemoreceptors and carotid bodies regulate the O_2 and CO_2 feedback mechanism. When there is low level of oxygen in the blood, a condition like hyperventilation gets developed against which carotid bodies get activated and the respiratory stretch receptors [14-16].

If the condition likes difficulty in breathing starts developing in this viral condition, then it can be reduced by two ways that are as follows: this virus directly attacked by angiotensin converting enzyme 2 expressing cells in the brain or else by the destructive effect of the cytokine storm which has the main role in sensing the difficulty in breathing [17].

Patient is the only one who detects the breathing pattern changes so therefore it is a totally a personal symptom [18]. The clinical features that are informed by relatives of the patient are as follows fast breathing, increased heart rate, altered facial expressions with difficulty in breathing. Which is not correct? Patients show different response in behaviour against any physical uneasiness or disease. If we take an example of pain, then the signs may come as extreme discomfort or with mild uneasiness [19].

There is this chief mediator for the deprivation of cells with the oxygen called as Hypoxic Inducing Factor 1 alpha. Proteasome destroys this factor which gives the undisturbed hypoxic state in the cell. The factor enters the nucleus and mediates the transcription of HRE genes that will results into various hypoxic conditions. Apart from this, it also facilitates transcription of some inflammatory genes by activating NF-kB factor. This is related to the increased serum ferritin deposition.

Early detection of hypoxia

There is the need of this silent hypoxia to be detected before the symptoms of breathing difficulty arise in patients with COVID-19. This is completely to sense the deteriorating levels of oxygen saturation before the patient goes under extreme case of pneumonia and he can be given best of the treatment before time. Also detecting the case at early stage prevents the usage of any invasive procedures to be done for e.g. intubation, mechanical ventilation.

But now there is this technology where smartphones have the application to detect the oxygen saturation. And it is also seen that the values compared to the pulse oximeter gives the accurate reading to that of the medical pulse oximeter. In normal individuals, the oxygen saturation lies in range of 95-100%. Therefore the population should be aware of this and should be promoted to use this regularly if there is any dip in the saturation level (95%).

This way of detecting the oxygen saturation on smartphones will result into early detection of silent hypoxia and also diagnosing the occurrence of pneumonia due to corona virus. This would ultimately decrease the intensive care entries, invasive procedures like intubation and also the death rate.

Now if we talk about the medical pulse oximeter, then it works by illuminating the skin and then due to the absorption of oxyhaemoglobin and low haemoglobin [20]. When we talk about the accuracy of the oximeter so there can be some percentage error which is <=4% [21]. It is considered that the blood oxygen saturation value <80% on oximeter will show less accurate reading because getting the human calibration value is difficult [22].

DISCUSSION

Other diagnostic factors

Blood gas analysis: The arterial blood gas analysis is an investigation in which a blood sample is collected from artery to detect the conc. of various gases in the blood. Appropriate processing of blood sample by this method gives different numbers of parameters for e.g. PaO_2 and $PaCO_2$ that are helpful to detect alkalosis, acidosis and also the silent hypoxia. Also newer studies have shown us that there are other parameters too which are helpful is diagnosis of this disease such as electrolyte balance, pH values, and bicarbonate values. The rise in value of $PaCO_2$ can precede the pH values along with the levels of electrolytes in blood. There is also a study which says that decreased values of parameters like potassium, calcium, sodium and pH is related to the severity of the disease and increasing death rate. Therefore, these two parameters pulse oximeter and blood gas analysis is important for the early diagnosis of silent hypoxia.

6 Min Walking Test (6MWT

There is one more way which can be helpful in detecting this case is the 6 min walking test. In this, the oxygen saturation value is seen after six minutes of walking. Then there oxygen saturation is compared with the saturation levels of the control group. This gives the amount of viral load in less severe to extreme conditions of COVID-19 patients. It is considered that if the distance covered by the person is less than 1400 feet in 6 min else the saturation level is dropping below 90% in this 6 mins should be considered as alarming conditions and need to be started with the appropriate intervention.

Effect of hypoxia on brain

The nerve conduction effectivity considered to be at least 30% to get an adequate oxygen supply to cerebral part of the brain. In case of its value decreasing below this will lead to hypoxemia that will result into reduced amount of adenosine triphosphate (<10%) within 5 minutes [23].

Patients suffering from novel corona virus showing moderate to severe drop in oxygen saturation level in the blood will result into multiple organ failure and also damages the central nervous system. This alters the sodium and potassium pump which is an oxygen sensitive channels and damage the neuronal and glial cells excitation and inhibition process. Also it activates the glutamate transporter which is responsible for the split of glutamate inside the synaptic area and causes toxicity of excitation of nerves [24]. In this condition, there is inhibition of kreb's cycle which leads to depletion of that molecule [25].

In condition of extreme low level of oxygen saturation, there is one factor (HIF)-1 gets balanced then there are genes which get expressed (e.g. erythropoietin, vascular endothelial growth factor, and insulin like growth factor 1) [26]. Adenosine which is a neuroprotective agent and also works as a neurotransmitter. Stimulation of this pathway will lead to activation of molecule phospholipase C; this restricts the release of molecule glutamate. Adenosine triphosphate which is present in the extracellular fluid breaks down into adenosine by HIF-1.

Mechanism of gut dysbiosis

There is this study which says that the microbes which are present in the gut and the host body show a symbiotic relationship which controls the process of metabolism of substances. These microbes can cross the blood brain barrier through the route of vagus nerve and can synthesize neuroactive molecules for e.g. Neurotransmitters, metabolites etc.

The gastro intestinal tract along with the angiotensin converting enzyme 2 expressing cells maintains the environment of the gut microbes by binding to the receptors of COVID-19 virus [26].

Differential diagnosis

The conditions which we can rule out on the basis of these clinical features were broad and are as follows: viral pneumonia, cardiogenic pulmonary oedema, pneumonia caused by atypical infection, and acute/ subacute hypersensitivity pneumonitis. In this condition of COVID-19, the patient with differential diagnosis fever, cough and type 1 respiratory failure has majorly influenced, that the above conditions can be considered as COVID-19 virus case until proved otherwise. The confirmatory basis of our diagnosis is nasopharyngeal and oropharyngeal swab for COVID-19 real time reverse transcriptase PCR and also the radiological finding. The factors like absence symptoms and signs, normal findings and electrocardiography findings exclude the evidence of heart failure. The chance of formation of emboli in any vessels of the lung which is not as common in patients with corona virus cases was excluded by imaging.

Treatment: After discussing all the areas of this condition, now the matter of fact is the management of this problem. So once the person suspect the clinical symptoms and suspecting this virus, visit to the nearest doctor. Now he will get the empirical therapy of hydroxychloroquine 400 mg/day for four days 2 times in a day on the very 1st day which will be followed by 400 mg/day again for the coming four days plus tab Azithromycin dose 500 mg/day for next five days. Heparin (low molecular weight heparin) will be given as 60 mg/day through subcutaneous route. Along with this, antitussives given for cough. He will be put on oxygen 15/L if respiratory distress persist along with this supplemental oxygen will be delivered by nasal canula. As soon as his condition will reverse (oxygen saturation crosses 94% and above, oxygen supply will be removed. Then a new specimen of oropharyngeal and nasopharyngeal swab will be taken to check the status [26].

CONCLUSION

The novel corona virus mainly attacks the cells of alveolar epithelium of the lungs and further transmitted

all over the body through the systemic blood circulation, neuronal pathway, it also attaches to angiotensin converting enzyme 2 expressing cells. It spreads through the pathways of olfactory epithelium in the central nervous system. The two classical factors–cytokine storm and direct neuro invasion to angiotensin converting enzyme 2 expressing cells in the limbic and insular area will lead to respiratory failure and happy hypoxia. Also, this will exaggerate neurological autoimmune diseases for e.g. Guillen barre syndrome.

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