Review Article

Rational use of oxygen and oxygen delivery devices in COVID 19

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Abstract

Oxygen is an emergency drug for respiratory patients with insufficient blood oxygen levels. Importance of oxygen in therapy increases in the recent pandemic. Around 5% of COVID19 patients develop respiratory distress due to immune-mediated diffuse alveolar damage and pulmonary microthrombi. In the grave crisis observed during the COVID 19 pandemic, knowledge of the rational and proper use of oxygen and oxygen delivery devices have become of utmost necessity. During treatment of a COVID19 patient, the dose of oxygen inhalation in litres/min and the choice of delivery device became crucial & it should be titrated with oxygen saturation (SpO2) of haemoglobin. A trial and error method for escalation-de-escalation of therapy should be followed to achieve the target SpO2 (92-96%). The objective is to achieve the target SpO2 with the minimum fraction of inspired oxygen (FiO2) to maximise efficacy and minimise oxygen toxicity. Nasal prongs, face mask, venturi mask, non-rebreather mask, high flow nasal cannula (HFNC) and Bi-level positive airway pressure (BiPAP) are the commonly used non-invasive devices for the delivery of oxygen. The maximum FiO2 achieved by these devices is 40, 55, 60, 100, 100 and 100 %, respectively. HFNC has an added advantage of delivering warm humidified oxygen which has respiratory epithelium protective effect. Patients not responding to conventional oxygen therapy can be given a trial of awake prone positioning to improve oxygenation. Similarly, BiPAP may be tried in conscious patients with preserved breathing strength, before the use of invasive mechanical ventilation (IMV) becomes inevitable. The majority of patients recover with proper and rational use of non-invasive oxygen therapy refuting the need for IMV which are associated with significant mortality and morbidity.

Keywords: Oxygen, Covid 19, non-invasive devices, Bi-level positive airway pressure

1. Introduction

The intensity and ferocity of COVID19 pandemic have shaken the world. During the "second wave" of the pandemic in India, the exponential surge in hospitalization in COVID 19 infection had choked the "oxygen line" of healthcare system. As per data available online with the website of Ministry of Health and Family Welfare, Government of India, the total number of deaths in India was 526033 (1.2 % of the total number of cases) as on 24rth of July, 2022 [1]. The cause of death in COVID19 is hyperinflammatory syndrome, primarily affecting the lungs leading to diffuse alveolar damage and microthrombi in pulmonary vasculature [2]. Patients requiring hospitalisation present with a rapidly progressing respiratory distress where oxygen inhalation is urgently required to save precious lives. Considering the acuteness and severity of such crisis, a clear and standard approach for rational use of oxygen and the oxygen delivery devices should be framed in preparedness of future exigencies of similar nature. In this article, we have described the principles of oxygen delivery and the proper and rational use of oxygen delivery devices in patients of COVID 19 presenting with hypoxia.

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Received 6th August 2022
Revised 10th October 2022
Accepted 11th October 2022
PHARMAWAVE 2022; 15:49-53.

2. Physiology of oxygen transport across the alveolo-capillary membrane

The movement of oxygen across the alveolo-capillary membrane occurs by simple diffusion. During inspiration, atmospheric air containing 21% oxygen gushes into the lungs due to the negative intra-thoracic pressure generated by the contraction of the inspiratory muscles. In the alveoli, the humidified air mixes with pre-existing alveolar gas. The concentration gradient of oxygen across the alveolo-capillary membrane is the driving force for delivering oxygen into the pulmonary capillaries[3]. In the inspiratory phase, the partial pressure of oxygen in the alveoli (PAO2) and the pulmonary arterial blood (PaO2) are 100 and 40 mm of Hg respectively, resulting in a diffusion gradient of 60 mm of Hg across the alveolo-capillary membrane.

The diffusion across alveolo-capillary membrane is perfusion limited because there is rapid equilibrium between alveolar oxygen and capillary oxygen. Apart from the oxygen gradient, diffusion of the volume of oxygen across the alveolo-capillary membrane is directly and inversely proportional to surface area and thickness of the alveolo-capillary membrane respectively [4].

3. Patho-physiology of hypoxia in COVID19

In majority of cases (around 80%), SARS CoV2 affects only the upper respiratory tract. It commonly presents as fever, malaise and cough and the patient recovers in a few days. However, seeding of the lower respiratory tract with the virus particle leads to extension of the infection to the lungs. The virus proliferates in the pneumocytes which in turn release large amount of cytokines. Cytokines recruit neutrophils and lymphocytes at the site of infection in the lungs. The so called "cytokine storm" refers to the uncontrolled and excessive release of cytokines, followed by a severe inflammatory state leading to damage to the alveolar cells. The phenomenon known as "diffuse alveolar damage" distorts the architecture of the alveolo-capillary membrane and decreases the rate of diffusion of oxygen into the pulmonary capillaries [5]. The inflammatory process also takes its toll on the pulmonary vasculature. In the initial phase of inflammation, the mediators, especially nitric oxide causes local vasodilatation of the pulmonary capillaries in the discretely scattered patches of "diffuse alveolar damage", producing areas of low ventilation/perfusion ratio, compared to the yet not involved areas where the ventilation/perfusion ratio is higher. The whole gamut of the heterogenous ventilation/perfusion mismatch leads to hypoxemia. In the later phases, the inflammation of the pulmonary tissue becomes more widespread and alveoli, interstitial and blood vessels are severely affected [6]. The endothelial cells of the blood vessels are damaged resulting in exposure of the thrombogenic basement membrane and activation of the coagulation cascade. Microthrombi are formed throughout the pulmonary vasculature[7]. Thus, diffuse alveolar damage and pulmonary microthrombi are the two main causes of hypoxia in COVID19.

4. Principle of oxygen delivery

Pharmacological intervention like anticoagulants to prevent microthrombi or steroids to dampen inflammation are aimed to correct the intrinsic pathological abnormality in the pulmonary tissue but cannot alleviate hypoxia in the acute setting. Increasing the fraction of inspired oxygen (FiO_2) during inspiration is the only rapidly acting intervention to correct hypoxia in COVID19 patients with pulmonary involvement [8]. Under normal condition of atmospheric temperature and pressure, the FiO2in the inhaled air is 21%. The FiO_2 can be increased up to 100% by administering oxygen through the inhalation route using oxygen delivery devices. The increase in FiO2 raises the partial pressure of oxygen in the alveolar air and oxygen is forced into the pulmonary capillaries driven by the steep trans-alveolar oxygen gradient. Despite altered permeability of oxygen across the deranged alveolo-capillary membrane, the increment in FiO2 produces a graded increase in blood oxygen levels at any particular condition of pulmonary involvement.

5. Non-invasive devices

Non-invasive oxygen delivery devices deliver oxygen through an outlet connected to an oxygen source, in the vicinity of nose or nostrils by non-injurious contact with the head and face, at specified rates of oxygen flow[9]. The popularly used non-invasive devices are nasal prongs, simple face mask, venturi mask, non-rebreather mask, high-flow nasal cannula and non-invasive positive pressure ventilation [9].

6. Nasal prongs

Nasal prongs are narrow-bored flexible tubes designed to deliver streamlined oxygen flow up to 5 litre/ min to the patient. While one end of the tube is attached to a graduated oxygen flow meter, the other end is split into two nozzles that loosely fits into the nostrils after snugly winding round the head of the patient. Beyond flow rates of 5 litres/min, the flow becomes turbulent leading to dissipation of delivered oxygen at the entry portal[10]. The PAO2 does not increase beyond what is achieved with 6 litres/min and there is no added clinical benefit to the patient. On the contrary, there is drying and thinning of nasal mucosa, occasionally leading to epistaxis. The FiO2 achieved by nasal prongs with 1 litre/min flow rate is 24%, increases by 4% with every litre increase in flow rate, and reaches a plateau at 44% with 6 litres/min, beyond which oxygen delivery with nasal prongs is not recommended [8].

7. Simple face mask

These devices are improvements over the nasal prongs where the patient end of the tube is expanded into a pyramidal semi-rigid hollow enclosure that fits over the nose and oral orifice. Oxygen is delivered at the rate of 5 to 10 litres/min, the face mask itself acts as a small functional reservoir of oxygen (of capacity 100-250 ml), resulting in an FiO2(35-55%) greater than what is achieved with nasal prongs (24-44%) [11]. Flow rates less than 5 litres/min are not recommended because there is rebreathing of trapped expired air from the functional reservoir leading to CO2 retention and aggravation of hypoxemia [12].

8. Venturi mask

These devices are improvements over the simple face mask where the oxygen inlet to the face mask is fitted with oxygen content regulators of varying capacity. The colour coded regulators (blue, white, orange, yellow, red and green) receive oxygen at incremental rates (2,4, 6, 8,10 and 15 litres/min respectively) and deliver fixed FiO2 of 24, 28, 31, 35, 40 and 60 percent respectively [8]. The FiO_2 can therefore be tightly

controlled as per need of the patient independent of the rate and depth of breathing [13].

9. Non-rebreathing mask

In these devices, the oxygen inlet to the mask is side-fitted with an inflatable oxygen reservoir bag. A flow rate of 10-15 litres/min is required to keep the bag in non-collapsed state. During inspiration, oxygen is sourced from the inflowing oxygen as well as from the reservoir, achieving an FiO2 of near 100% depending upon the flow rate [14].

10. High flow nasal cannula

It is an electromechanical device that generates an admixture of warm humidified air containing oxygen of desired concentration [15]. To avoid water-vapour condensation, the admixture is delivered with a help of heated inspiratory circuit terminating in a nasal canula with wide bores that fits snugly into the patient's nostrils[16].The maximum rate of gas delivery achievable with the device is 70 litres/min with an FiO2 of up to 100% [10]. Despite the high flow rate, humidification of the gas mixture ensures that the adverse effects of mucosal drying, erosion or bleeding are minimal.

11. Non-invasive positive pressure ventilation

It is also an electromechanical device that delivers air-oxygen mixture of desired FiO_2 at adjustable positive airway pressure (PAP). The inspiratory circuit ends in a soft but non-deformable mask that tightly seals over the face covering the nose and mouth [17]. The PAP is administered in two ways-continuous positive airway pressure (CPAP) and Bi-level positive airway pressure (Bi-PAP). While CPAP is primarily used in obstructive sleep apnoea to splint open the airway during sleep, Bi-PAP has more diversified applications in acute respiratory failure secondary to asthma, COPD, pulmonary oedema, pneumonia and others [18].

12. Invasive devices

12.1 Mechanical ventilation

The non-invasive devices may not achieve adequate oxygenation in severely ill patients with heavily incapacitated respiratory effort. Similarly, patients with diminished sensorium may become susceptible to respiratory depression and aspiration. The invasive method of endotracheal intubation and mechanical ventilation not only protects airways but also is the most efficient modality for elevating and maintaining oxygen levels in such critically ill patients. However, like any other invasive device, endotracheal intubation also inflicts an injury to the natural barrier epithelium (here, respiratory epithelium) and predisposes the individual to secondary infections [19].

12.2 Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation is the end-option inpatients with unimproved blood oxygen levels despite the initiation of mechanical ventilation. In this method, venous blood is fully saturated with oxygen by circulating through a membrane oxygenator at a maximum rate of 4 litres/min [3].

13. Guidelines

Patients presenting with shortness of breath should be immediately assessed for hypoxemia using clinical and blood parameters. The measurement of haemoglobin saturation with a pulse oximeter is a very useful, point-of-care, non-invasive tool for assessment of blood oxygen levels. It is a close surrogate for partial pressure of oxygen in the arterial blood up to 100 mm of Hg. In the emergency setting, it guides the empirical initiation of oxygen administration, the rate of oxygen flow and the choice of delivery device. Since pulse oximetry is non-invasive and innocuous, it is also very useful for titration of rate of oxygen flow. In the strained state of logistics during the COVID 19 pandemic, this simple device guided the escalation and de-escalation of oxygen therapy and the oxygen delivery devices with reasonable accuracy. The arterial blood gas analysis which depicts the accurate picture of the respiratory gases in blood is invasive and repeated arterial puncture have practical limitations. As per the World Health Organization (WHO), the target SpO2 in COVID19 patients should be more than 90% and between 92-95% in adults and pregnant women respectively [20].The Surviving Sepsis Campaign (SSC) COVID-19 guidelines recommended that supplemental oxygen should be initiated at SpO2 below 92% and adjusted thereafter, to maintain a target SpO_2 of 92-96%[21]. Saturation greater than the recommended levels is not only a waste of resources but also deleterious to the patient and may produce adverse effects [22]. The objective is to achieve the target saturation with the minimum FiO_2 of oxygen with the correct choice of the delivery device. While seriously ill patients with poor breathing effort, severe respiratory distress, obtunded sensorium or convulsion, may need urgent endotracheal intubation and mechanical ventilation as a life saving measure, the trial of non-invasive ventilation should be accorded to all patients irrespective of the oxygen saturation. As a rule of thumb, the initiation of supplemental oxygen in patients with saturation 90-92%, 85- 89 % and <85% should be with nasal prongs, face mask/venturi mask and non-rebreather mask/high flow nasal cannula, respectively. A step wise escalation-de-escalation of oxygen therapy should be implemented by trial and error to achieve the target saturation [23]. The incremental order of FiO2 delivery with the non-invasive devices is nasal prongs, face mask, venturi mask, non-rebreather mask and high flow nasal cannula. Both high flow nasal cannula and BiPAP can deliver equal amount of FiO2, but the high flow nasal cannula is preferred over non-invasive positive pressure ventilation because it can deliver warm humidified oxygen at very high flow rates (up to 60 litres/min). Patients not responding to conventional oxygen therapy should be given a trial of awake prone positioning (in patients who can tolerate) before going for invasive mechanical ventilation [24]. Mechanical ventilation is a skilled intervention and requires trained personnel and equipped critical care units for effective running. Finally, the existing evidence for use of extracorporeal membrane oxygenation in COVID19 respiratory failure are not robust enough to support or refute their use in the most critically ill patients failing to maintain arterial oxygen levels even with mechanical ventilation [25].

14. Oxygen as a drug

In physiological conditions, oxygen is a naturally occurring atmospheric gas that is inhaled by living organisms and utilised for aerobic metabolism- life processes that are of immediate necessity for the sustenance of life. In COVID19 infection with respiratory illness, oxygen is the indispensable, emergency-purpose, life-saving drug administered through inhalation

route. The pharmacokinetics of the drug mimic the natural physiological process of oxygen transport. After inhalation, oxygen diffuses across the alveolo-capillary membrane, is transported in blood in dissolved and bound form (with haemoglobin) and finally reaches the site of action (mitochondria and cytoplasm) in every living cell of the body. Oxygen is metabolised to carbon dioxide inside the cell and a reverse transport carries carbon dioxide to the plasma for elimination by the lungs (majority) and the kidneys (a small fraction). Failure to initiate oxygen therapy in patients needing it, leads to rapid deterioration and irreversible systemic changes causing profound morbidity and mortality. [23].

15. Adverse effects of oxygen inhalation

Sustained high levels of oxygen in blood induces injurious effects on the bio-metabolic processes. In the mitochondria, reactive oxygen species are generated leading to activation of apoptotic pathways, loss of cellular homeostasis and cell death. Reactive nitrogen species secondary to oxidant stress are produced, the production of nitric oxide decreases causing vasoconstriction and diminished tissue perfusion [26]. The pulmonary epithelium and the surfactant layer can be damaged leading to atelectasis and further deterioration of the respiratory pathology. The central nervous system can also be affected leading to altered sensorium, convulsion and even coma. High levels of oxygen can suppress the respiratory drive leading to carbon dioxide retention and narcosis. Retrolental fibroplasia and retinal toxicity may also occur [27]. Rational therapy with oxygen, utilising correct dose and duration of the drug has hugely positive biological effects in the individual and causes the least adverse effects. Oxygen is a powerful drug that should be administered with strict monitoring to prevent dosing errors and titration of oxygen therapy with blood oxygen saturation should be strictly adhered [26].

Conclusion

Oxygen is a life-saving drug. The judicious and rational use of oxygen therapy with the appropriate delivery device can hugely reduce the morbidity and mortality associated with COVID19 and future pandemics of similar nature.

Acknowledgement:
Authors declared no acknowledgement.

Conflict of Interest
The authors proclaim no conflict of interest

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