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Meta-Analysis - Prevention of Oxygen Toxicity in COPD Patients with Hypercapnia

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Abstract

All mammalian species including humans are dependent on oxygen for their existence. The oxygen required within the body is inhaled from the atmosphere and exchanged with exhaled carbon dioxide resulting from various metabolic processes. The malfunctioning of the respiratory system involved with inhaling of oxygen leads to a number of diseases known as a chronic obstructive pulmonary disease (COPD), and artificial supply of oxygen is required to compensate for lower levels of oxygen for certain patients. Imbalances in the provision of necessary oxygen in certain circumstances generate higher levels of carbon dioxide known as hypercapnia resulting subsequent to oxygen therapy among COPD patients. Higher levels of oxygen known as hyperoxia have also been reported associated with oxygen treatments. Both the hypercapnia and hyperoxia in the COPD patients are related to the deleterious effect on the cognitive functions and pulmonary complications. Furthermore, reactive oxygen species resulting from hyperoxia induce unwanted apoptosis in healthy tissues of various organs. This article reports a meta-analysis of four cross-sectional studies demonstrating oxygen therapy among COPD patients manifested hypercapnia, and interventions to minimize such detrimental effects. Based on the evaluation of data from these studies it is recommended that non-invasive intervention (NIV) coupled with long term oxygen therapy (LTOT) enhances the survivability of COPD patients with hypercapnia, thereby eliminating any instance of mortality, with a compromised quality of life. Furthermore, usage of NIV or noninvasive positive pressure ventilation (NPPV) is an effective control of oxygen toxicity in COPD patients with hypercapnia. It is also recommended that in oxygen therapy, the oxygen pressure in the blood (PaO_2) should be maintained between 7.3 and 10 kPa (kilo Pascal) with a SaO_2 (hemoglobin bound oxygen) of 85 - 92%. The titrated oxygen treatment instead of high flow oxygen is beneficial for the overall better outcomes. These recommendations have practical implications for health care professionals using oxygen therapy among COPD patients.

Keywords: *Oxygen Toxicity; Oxygen Therapy; Chronic Obstructive Pulmonary Disease (COPD); Hypercapnia; Hypoxia; Hypoxemia*

Introduction

In clinical practice, oxygen therapy is usually prescribed for the people unable to get oxygen due to in diseases like chronic obstructive pulmonary diseases (COPD) used to describe a set of clinic condition having a deformity in the physiological functioning of lungs [1]. Oxygen therapy is also administered in several other emergent conditions involving acute respiratory failure inflicting dyspnoea associated with lowered levels of oxygen in the blood [2,3]. Treatment with an external supply of oxygen can be for a short time like carbon monoxide poising [4] in which the patients' blood oxygen level drops significantly or for a longer period of time as in the COPD [5]. Particularly, a randomized trial of long term oxygen treatment (LTOT) for COPD patients funded by the National Heart Lung and Blood Institute (NHLBI) of the US National Institutes of Health (NIH) conclude "In patients with stable COPD and resting or exercise-induced moderate desaturation, the prescription of long-term supplemental oxygen did not result in a longer time to death or first hospitalization than no long-term supplemental oxygen, nor did it provide sustained benefit with regard to any of the other measured outcomes [6,7]". This and several other studies have raised questions about the usage of LTOT and its overall implications on the patient quality of life and ultimate outcome. Although a focused group workshop held under the aegis of the NHLBI highlighted the beneficial usage of LTOT in COPD patients prolonging and improving the quality life [8]. This paper also raised the question relevant to the paucity of current research on LTOT in the management of COPD and the overall cost versus benefits. Future clinical trials recommended in this paper relevant to patients suffering from the COPD were in the area of "1) efficacy of ambulatory O(2) supplementation in subjects who experience oxyhemoglobin desaturation during physical activity but are not severely hypoxemic at rest; 2) effectiveness of LTOT in subjects with severe COPD and only moderate hypoxemia; 3) efficacy of nocturnal O(2) supplementation in subjects who show episodic desaturation during sleep that is not attributable to obstructive sleep apnea; and 4) effectiveness of an activity-dependent prescription for O(2) flow rate that is based on clinical tests performed at rest, during exercise, and during sleep [8]". Several previous and current studies report that oxygen therapy reduces COPD complications by stabilizing pulmonary hypertension [9], decreasing arrhythmias [10], reducing instances of secondary polycythemia [11], as well as preventing myocardial ischemia [12]. Also, it lowers and relieves instances of dyspnea, as well as other symptoms that are related to COPD, such as depression, dizziness, and fatigue [13].

There are instances of oxygen toxicity which can arise during oxygen therapy and are mainly associated with uncontrolled oxygen administration to patients either with COPD or other oxygen needing treatments [14,15]. Continued oxygen therapy has always been considered as a tedious clinical decision and due to issues with ventilation perfusion inequalities caused hypoxemia that varies from person to person and physiological condition ultimately leading to higher arterial PCO2 (hypercapnia) [16]. In clinical evaluations, the level of hypoxemia can be used as a predictor for the subsequent development of hypercapnia. Under rare circumstances, noninvasive ventilation for either pediatric or COPD patients encounter an apneic response in patients that are approaching a hypercapnic coma [17-19]. In essence, the adverse effects linked to inappropriate oxygen therapy include muscle twitching, headache, coma, and even, in some cases, death [20,21]. These and several other studies, including recent past clinical trials have raised questions about the utilization of oxygen therapy in the COPD and other oxygen requiring ailments. This papers describes and in depth analysis relevant to COPD patients at risk of developing carbon dioxide retention from the administration of oxygen therapy, mainly caused by hypoventilation.

Background of the Study

The Paul Bert clinical observations published in a book "La Pression Barometrique" in the last century are considered seminal in describing oxygen pressure association with life [22,23]. His work suggests that patients exposed to 15 - 20 ATA (atmosphere absolute) had convulsions. Among several others, a study by Chawla and Lavania, suggest that molecular oxygen required for our sustenance become toxic at higher partial pressures [24]. The major manifestation of these toxicities is in the form of central nervous system abnormalities, pulmonary deficit and ocular complications among infants subjected to elevated oxygen pressures. The CNS complications associated with oxygen pressure imbalances are referred to as the "Bert effect [25]". Later in an effort to reconfirm Bert effect, researchers observed that fatal pneumonia in mammalian species could also be an indication observed at 73% oxygen at one ATA. Patel., *et al.* further elaborates on the oxygen toxicities and classify them into two groups, i.e. acute and chronic dependent on short term and long term administration of oxygen respectively [25].

Studies have shown that oxygen saturation (SpO_2) plays a significant role in the overall outcome relevant to oxygen therapy [26]. In UK, a national early warning score (NEWS) has been used for surveillance of patients having issues with oxygen distribution within the body. Values below 96% SpO_2 are considered as risk warnings and values between 88 - 92% are required for survival of the patient. However, data shows that NEWS is unable to accurately predict SpO_2 among patients suffering from hypercapnic respiratory failures in cases like COPD [27,28]. These circumstances suggest alternative measures to monitor patients with hypercapnia and respiratory illnesses, particularly COPD patients on the oxygen therapeutic regimen.

Oxygen therapy has also been reported to induce hyperoxia [29,30], that leads to the formation of reactive oxygen species (ROS) including superoxides, hydrogen peroxide, single oxygen, as well as hydroxyl radicals [31]. These ROSs are usually generated through a variety of cellular enzymes, ionizing/ultraviolet radiation, and mitochondrial metabolism. Importantly the ROS species have deleterious effects on biological systems and various organs through inflicting damages at cellular levels [32]. For this reason, oxidative injury, which culminates from oxygen poisoning, can induce a necrosis of human cells or apoptosis. Furthermore, increased oxygen concentrations can increase inflammatory responses through the reduction of tissue hypoxia and levels of the hypoxia-inducible factor 1a, a regulatory molecule generated in hypoxic environments [31].

All this allude to the fact that oxygen toxicity can have adverse effects at cellular and tissue levels expanding to organs. Complications associated with the breathing of molecular oxygen, mainly in reference to partial pressures negatively impact the lungs, eyes, and other organs to systems. The central nervous system (CNS) toxicity is the prominent feature of oxygen toxicity occurring at pressures of greater than 3 ATA [24]. When oxygen therapy is provided at lower pressures for prolonged periods, similar adverse effects are also experienced, as shown in Figure 1 below. Even though there are various early symptoms associated with CNS toxicity, twitching of perioral and small muscles is a common feature, but "cogwheel" breathing, as well as facial pallor, can accompany the symptoms, caused by diaphragmatic twitching and hyperoxia, respectively [24,25]. The continuity of adverse condition can lead to coma and death. Further, according to Barjaktarevic and Cooper [31], acute exposure to high partial pressures associated with CNS oxygen toxicity may occur for patients undergoing hyperbaric oxygen therapy (HBOT), as well as divers. Importantly, hyperoxia results in retrolental fibroplasia [33]. Importantly, lungs are prone to injury during instances of elevated oxygen partial pressure, and can also suffer from pulmonary toxicity [34]. The major early signs of pulmonary toxicity are tracheobronchial irritation, which is coupled with pleuric or sub-sternal chest pain, ARDS, as well as pulmonary interstitial fibrosis [24]. In addition, absorption of atelectasis which emanates from the N_2 washout can cause parts of the lungs to collapse where air trapping occurs.

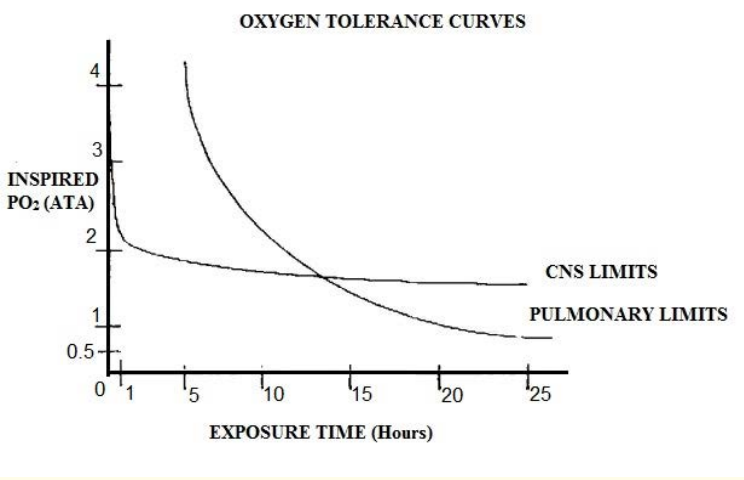

Figure 1: *The predicted human pulmonary and CNS tolerance to inspired oxygen at high pressures. Source: by Chawla and Lavania [24].*

Objective and Justification of the Study

Given the adverse effects associated with oxygen toxicity, as highlighted in the introduction and background of this paper, it is critical to identify clinical intervention for proper management of oxygen therapy among COPD patients with hypercapnia. This will involve managing oxygen toxicity, which is purely symptomatic, should be prioritized once the symptoms are diagnosed or observed. Importantly, when the oxygen therapy is stopped abruptly at the onset of the symptoms, toxicity may aggravate these symptoms, referred to as the "oxygen off effect," and this needs to be taken into account when preventing instances of oxygen toxicity among COPD patients with hypercapnia. In essence, hypercapnia, that raises the levels of carbon dioxide (CO_2) in the blood, can cause headaches, drowsiness, confusion, lethargy and, in severe cases, it can result in coma and death [35]. The COPD patients with hypercapnia are flushed and warm to touch, which may be accompanied by "flapping tremors" of the hands. It should also be noted that too much supplemental oxygen can cause or worsen hypercapnia via different mechanisms, such as intensely changing the relationship of air exchange within the lungs and blood, reducing the drive to breathe, and a risk of oxygen and carbon dioxide binding with hemoglobin in the red blood cells. For this reason, there is a need to prevent oxygen toxicity in these instances. Based on the current data relevant to oxygen treatment, the aim of this meta-analysis is to assess the various methods of preventing oxygen toxicity, that will save patients from the risks of CNS and pulmonary issues that become lethal in severe circumstances. The following is an overview of the principal and secondary objectives guiding this meta-analysis:

1. To provide an overview of the oxygen toxicity among COPD patients with hypercapnia.
2. To review the literature regarding oxygen toxicity among COPD patients with hypercapnia, highlighting complications and adversities.
3. Evaluating cross-sectional studies that relate to the prevention of oxygen toxicities and the interventions adopted.
4. Devising key recommendations regarding the prevention of oxygen toxicity.

Literature Review

Chronic obstructive pulmonary disease (COPD) is a term used to describe several lung diseases like asthma (refractory), chronic bronchitis, emphysema, and several types of bronchiectasis. The hallmark of disease manifestations is elevated breathlessness and is considered a major public health concern globally [36]. The global burden of the COPD is very high [37]. The World Health Organization (WHO) estimates that on the average 210 million people have had moderate to severe cases of COPD, and many people die of the condition annually [38]. In spite of the control over risk factors like smoking the morbidity and mortality associated with the COPD are significantly higher [39]. The COPD associated respiratory ailments affect the overall national economy through impact the performance of individuals serving with this disease.

Although several treatments are available for overcoming COPD, however, oxygen treatment is considered one of the choice treatments for acute cases and particularly during emergency situations. Unfortunately, oxygen treatment is highly technical in nature, both the over and under dosing lead to detrimental effects on the patient being treated. The high flow oxygen among normal people leads to an increase in minute ventilation, which is the volume of air that is inspired or expired out of the lung within a minute, accompanied by a decrease in the concentration of tidal carbon dioxide [38]. As noted earlier, oxygen toxicity leads to CNS and pulmonary toxicities, which may result in death.

Patel., *et al*. [25] assertion based on the existing scientific information reports carbon dioxide narcosis in patients with COPD, primarily because alveolar ventilation is inadequate to prevent rising levels of arterial carbon dioxide pressure ($PaCO_2$). The resulting increased hypercapnia, which emanates from higher levels of $PaCO_2$, the respiratory center becomes progressively more tolerant to levels of CO_2, and thus, its activity is maintained by the stimulus of hypoxemia through aortic and carotid bodies. The removal of this stimulus through the administering of oxygen reduces the ventilation further, leading to an increase of $PaCO_2$, as well as carbon dioxide narcosis coupled with raised intracranial tension, manifested through a variety of symptoms. These include convulsions, papilledema, drowsiness, twitching, and can also result in coma, and, thus, carbon dioxide narcosis is a potentially lethal condition owing to oxygen toxicity [40]. As such, researchers have asserted that there is a need for the monitoring and prevention of oxygen toxicity, such as avoiding instances of "oxygen off effect" where there is a sudden stoppage of oxygen therapy.

The oxygen toxicity is associated with reducing the vital capacity of an individual receiving treatment that is used as an indicator to monitor instances of pulmonary toxicity and has leverage for 10% acceptable reduction. Besides, dynamic lung compliance, as well as the diffusing capacity for carbon monoxide (DLCO) should also be monitored and reduced to acceptable limits to halt oxygen toxicity. In addition, to predict an instance of pulmonary damage due to supplemental oxygen, a unit of pulmonary toxicity dosage (UPTP) is often calculated where a 100% supplemental oxygen at one atmosphere is taken for producing one UPTD. Furthermore, the data suggest a UPTD of 1425 provides a 10% reduction in vital capacity [25].

Maintaining PaO_2 at levels greater than 50 mmHg is considered safe for patients suffering from COPD, whereas higher levels deteriorate cognitive functioning, as well as preventing instances of transient desaturations [41]. For patients with COPD, it is advisable to use a concentration of oxygen that can subsequently compensate dangerous levels of PaO_2 [25]. Patel., et al. report is further substantiated by another study indicating that the exact amount of PaO_2 that is dangerous is unclear, but most importantly, COPD patients should be adequately oxygenated, and their PaO_2 levels should be above 50 mmHg [42]. The authors of this study also suggest that the most dangerous effects of CO_2 retention are depression of cardiorespiratory and neurological functioning, and points out that a rising $PaCO_2$ followed by decrease pH are usually fatal [9,42]. Additionally, positive end-expiratory pressure (PEEP) needs to be utilized during instances of mechanical ventilation if an inspired concentration of oxygen is kept greater than 50% to relieve dangerous levels of hypoxia, and can be particularly important for patients with COPD [25]. For acute pulmonary problems with severe hypoxia, oxygen saturation should be greater than 90%, and efforts should be directed toward maintaining levels of PaO_2. The lower limit of PaO_2 in oxygen therapy is 55 mmHg, which is mostly used as entry criteria for LTOT trials [41]. Besides this, real-time monitoring of PaO_2 is not always possible, and thus, targeting a SaO_2 range of between 88% and 92% is used for COPD patients with a risk of hypercapnia.

Oxygen administration in COPD patients induces hypercapnia mainly via the hypoxic drive mechanism, which can be dangerous [43]. Patients who have a high susceptibility to oxygen-induced hypercapnia are those with severe instances of hypoxemia, and, for this reason, administering titrated oxygen with an oxygen concentration of between 88% and 92% is better compared to higher levels, which results in less respiratory acidosis and a better outcome. In addition, for patients with COPD, hypoxic pulmonary vasoconstriction can be the best option for improving gas exchange, achieved by altering Va/Q ratios [43].

In a meta-analysis by Abroug., *et al.* [44], when helium-oxygen (He/O_2) mixture is used as a driving gas during noninvasive ventilation (NIV) in hypercapnic COPD exacerbation, it reduces gas trapping and positively impacts breathing. In this study, it has also been reported that, compared to air/O_2, He/O_2 does not reduce the rate of NIV failure in COPD patients with hypercapnia, but is associated with lower instances of NIV-related adverse events, as well as shortening the length of stay in an ICU without increasing hospital costs.

Methodology

The study utilizes a meta-analysis approach mainly focusing on cross-sectional studies related to the topic of oxygen toxicity in the COPD. The first part of the meta-analysis is a systematic review of the key concepts related to oxygen toxicities in COPD patients with hypercapnia. The analysis is based on searches conducted in the main medical databases, including PubMed, that provides free access to the MEDLINE and the National Library of Medicine database including citations and abstract of studies in the field of medical, nursing, dental, veterinary, health care, and preclinical sciences journal articles [45]. The search criteria are designed in a way that it identified article describing hypercapnia with the use of oxygen therapy among COPD patients. A set of search phrases were used including i) oxygen toxicity in COPD patients, ii) oxygen therapy in patients with hypercapnia, iii) prevention of oxygen toxicity in COPD patients, and iv) prevention of hypercapnia using oxygen therapy. The focus was only to identify studies utilizing cross-sectional design.

Results and Discussion

Based on our highly meticulous selection criteria four cross-sectional studies matched with our requirements describing comparative assessment of COPD patients with hypercapnia. These studies also illustrate how oxygen was clinically administered to prevent CNS and pulmonary toxicities caused by oxygen therapy. Overall, this meta-analysis is based on data from all these four studies. Several other stud-

ies have addressed the topic. However, the rest do not fulfill the requirements of our criteria. A description relevant to these studies is as in the following:

One of the largest randomized, controlled trials of non-invasive bi-level positive pressure oxygen treatment in stable end-stage hypercapnic COPD was conducted by McEvoy., *et al* [46]. This study hypothesized that sleep hypoventilation causes progressive hypercapnic respiratory failure as well as death in patients with severe instances of COPD. As such determination of the effects of nocturnal non-invasive bi-level pressure support ventilation (NIV) on survival, lung functionality, as well as the quality of life for COPD patients with severe hypercapnia [46]. Being a multicenter, open-label, and randomized trial of NIV and LTOT versus LTOT alone, the patients had severe stable smoking-associated COPD with forced expiratory volume of 1 s ($FEV_{1.0}$) <1.5 liters and $FEV_{1.0}$ to forced vital capacity (FVC) of < 60% with $PaCO_2$ > 46 mm Hg and being subjected to LTOT for about three months. All study participants were less than 80 years old. A total of 144 study participants were randomized, and 72 being subjected to NIV and LTOT and the remaining 72 to LTOT alone. The results showed that NIV along with LTOT improved the quality of sleep and hypercapnia compared to LTOT alone. Further, the evaluation revealed that NIV along with LTOT enhances the survivability of COPD patients with hypercapnia and not the quality of life for the patients suffering with respiratory distress.

The second cross-sectional study matching with our selection criteria is a study by the Budweiser., *et al*. [47] that describes the predictors of survivability of COPD patients with hypercapnia, it was observed that patients with COPD and chronic hypercapnic respiratory failure (CHRF) are mainly at a higher risk, thereby necessitating the use of noninvasive ventilation in home settings. A total of 188 study participant with COPD receiving FEV1.0 (31%) and $PaCO_2$ (56.3%) and discharged from hospital and receiving NIV between July 1994 and July 2004 were assessed using multivariate and univariate Cox regression analysis. After follow-up, the mortality rate after 32.2 - 56.4 months was 44.7% with 1-, 2-, and 5-year survival rates of 84%, 65.3%, and 26.4%. It was also noted that in the majority of the cases deaths resulted from respiratory failure (73.8%). In the study, univariate regression analysis showed that age, BMI, FEV_1, residual volume (RV), pH, and base excess (BE) were associated with prognosis while multivariate prognosis identified that BMI, age, RV, and BE were independent predictors. Furthermore, for patients at risk with BMI of less than 25km/m^2 and RV of greater or equal to 73% and a BE of greater or equal to 9 mmol/L, changes in predictors were associated with higher survivability. As such, it was concluded that, for CHRF and COPD patients, nutritional status, BE, and hyperinflation were independent prognosis factors for mortality. Therefore, for effectiveness in dealing with COPD, use of noninvasive ventilation is important [47].

The third cross-sectional study of this meta-analysis is by Plant., *et al.* [48] describing the prevalence of respiratory acidosis in acute COPD over a period of one year suggesting the importance of noninvasive ventilation (NIV), as it reduces intubation rates and mortality in patients with COPD while drawing inferences from oxygen therapy. Study participants ages range 45 - 79 years and were from typical UK hospitals, such as St. James University and Leeds Infirmary, enrolled during 1 March and 28 February 1998. Among the 983 patients admitted, 11 needed immediate intubation while 20% of the remainder had respiratory acidosis [48]. Researchers believe that acidosis was associated with admissions to ICU, particularly for those patients with a pH < 7.25 and pH 7.25 - 7.30. As such, pH was inversely correlated with PaO_2 in 47% of hypercapnic patients, with PaO_2 > 10 kPa being associated with acidosis for most COPD patients with hypercapnia. Eighty percent of the patients remained acidotic after the first treatment, and thus, NIV was necessary as a typical UK hospital admits 90 patients annually and of that, 72 needed NIV. For this reason, it was concluded that, for patients with acute COPD, PaO_2 should be maintained at between 7.3 - 10 kPa and with a SaO_2 of 85 - 92% to avoid acidosis and hypoxia.

The fourth study aligning with our criteria is by Austin., *et al*. [38] describing the impact of high flow oxygen on mortality in COPD patients in pre-hospital settings compared with standard high flow oxygen treatment for patients with acute COPD. Using a randomized, controlled trial, 405 COPD patients were treated and admitted to Royal Hobart Hospital. Two hundred and fourteen patients had COPD in the five years prior. The primary outcome measure was mortality, among the patients, the risk of death was lower in the patients receiving titrated oxygen (n = 179) arm compared with the high flow oxygen (n = 226) arm, and overall mortality was 9% in the high flow oxygen arm and 4% in the titrated oxygen arm. In the subgroup with COPD, high flow oxygen had a death rate of 9% while 2% of patients

administered with titrated oxygen died. As such, titrated oxygen in the study reduced mortality compared to high flow oxygen by almost 58% for all patients and by 78% for COPD patients, and, thus, they were less likely to have respiratory acidosis or hypercapnia. As such, titrated oxygen treatment reduced instances of hypercapnia, mortality, and acidosis compared to high flow oxygen.

Assessment Factor	McEvoy *et al.* (2009) [46]	Budweiser *et al.* (2007) [47]	Plant *et al.* (2000) [48]	Austin *et al.* (2010) [38]
Patients	144	188	983	405
Condition addressed	COPD, Progressive hypercapnic respiratory failure, and mortality among COPD patients.	COPD, chronic hypercapnic respiratory failure (CHRF).	Respiratory acidosis in acute COPD, COPD patients with hypercapnia.	Mortality in COPD patients in pre-hospital settings
Intervention	NIV coupled with LTOT increased survivability.	Use of Non-invasive intervention or noninvasive positive pressure ventilation (NPPV)	PaO_2 should be maintained between 7.3-10 kPa and SaO_2 of 85-92%.	Titrated oxygen treatment instead of high flow oxygen.

Table 1: *Comparative Assessment of Cross-Sectional Studies.*

Proposed Guidelines

Based on the evaluation of four cross sectional studies several facts glean out as far as oxygen therapy in COPD patients is concerned. First, to improve survivability, NIV coupled with LTOT is proposed, however, to improve the quality of life, use of LTOT alone is recommended [46]. Additionally, He/O_2 compared to air/O_2 does not reduce the rate of NIV failure in COPD patients with hypercapnia but is associated with lower instances of NIV-related adverse events, as well as shortening the length of stay in an ICU without increasing hospital costs. Besides, NPPV and NIV are recommended to enhance the survivability of patients with hypercapnia. The BMI, FEV_1, residual volume (RV), pH, age and base excess (BE) should be included in diagnosing CHRF to ensure that the patient has an increased likelihood of surviving. For controlling oxygen toxicity, it is important to make sure that PaO_2 is maintained between 7.3 and 10 kPa and SaO_2 between 85 and 92%. In addition, using titrated oxygen treatment for the administration of supplemental oxygen therapy is recommended instead of high flow oxygen as it would eliminate instances of respiratory acidosis. For patients receiving LTOT, it is recommended that the lower limit of PaO_2 (55 mmHg) is used in oxygen therapy [41].

Limitations of the Study

The results of this meta-analysis provide critical recommendations the prevention of oxygen toxicity in spite several limitations. These recommendations are based on secondary analysis, and the authors do not have in depth knowledge relevant to study biases. The results/outcome of this study are based only on the search criteria and the inclusion and exclusion strategies used. If any of the studies has certain limitations, their controls is beyond our evaluations. These recommendations are based on the pre-existing data and not the findings generated in the laboratory. Moreover, the paper was based on four cross-sectional studies, thereby limiting the level of validity and reliability of the comparative assessment carried out in this article. Furthermore, the research topic has not been studied extensively, which led to limited publication results from the consulted databases meaning that future studies should cover more cross-sectional studies.

Conclusion

Oxygen therapy can result in oxygen toxicity, especially for COPD patients with hypercapnia. As such, there is a need for prevention of oxygen toxicities. Uncontrolled oxygen administration is associated with an early initial decrease in minute ventilation, characterized by an elevation of $PaCO_2$. However, oxygen administration in acute exacerbation of severe COPD has a limited effect on instances of minute ventilation, and, for this reason, a total increase of $PaCO_2$, exerts CNS or pulmonary toxicities. This can subsequently induce hypercapnia among COPD patients, which is characterized by adverse symptoms, including nausea and vertigo, followed by clumsiness, altered

behavior, and, finally, convulsions or death. It is mandatory that clinical use of oxygen therapy should be aimed at controlling toxicities associated with its usage.

This study concludes by proposing several practical strategies for overcoming oxygen toxicity while using oxygen therapy among COPD patients. These include i) NIV coupled with LTOT to increase the survivability of COPD patients with hypercapnia, thereby eliminating any instance of mortality, but this can provide a compromised quality of life, meaning that LTOT can be used instead, particularly when the patient is expected to survive; ii) the use of non-invasive intervention (NIV) or noninvasive positive pressure ventilation (NPPV) is an effective control of oxygen toxicities among COPD patients with hypercapnia. In clinical use of oxygen therapy, it is important to ensure that PaO_2 is maintained between 7.3 and 10 kPa and SaO_2 between 85 and 92%; iii) the use of titrated oxygen treatment instead of high flow oxygen is recommended. These strategies will help reduce the adversities associated with the administering of supplemental oxygen or oxygen therapy.

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