RESEARCH PROPOSAL

REVIEW ON OXYGEN THERAPY IN COPD PATIENTS – MYTHS AND EVIDENCES

INTRODUCTION

The administration of oxygen to the patients with chronic obstructive pulmonary disease (COPD) has been a matter of clinical concern since decades. It is believed that administering the oxygen to these patients will reduce the "hypoxic drive" nothing but the drive to breath. This hypoxic drive theory has been controversial since decades and posing a dilemma to the medical and nursing professionals. This review aims to prove the fact that oxygen administration does not reduce the hypoxic drive in COPD patients by reviewing different evidence based studies.

REVIEW OF LITERATURE

Theoretical framework

Patients with COPD suffer from chronic inflammatory changes which lead to the destruction of airways, pulmonary blood vessels and the parenchyma. (Kent et al., 2011) Scarring and fibrosis of the smooth muscles and the connective tissues lead to compromised gas exchange. This increases the levels of carbon dioxide in the blood of these patients. In normal healthy people, the drive to breath comes from the high levels of carbon dioxide in the blood. Whereas in COPD patients, the high levels of carbon dioxide compromise the function of carbon dioxide chemo receptors, resulting in the drive to breathe dependent on oxygen chemoreceptor's response to low level of oxygen. This phenomenon is termed as 'hypoxic drive'. (Kent et al., 2011)

Hypoxic drive theory- Myths and clarifications

According to this theory, the levels of oxygen increase in blood when a patient with COPD is administered oxygen. This increase in the oxygen levels may signal the body to stop breathing, which may lead to the death of the patient.

Hoyt 1997 explained the mechanisms by which the hypoxic drive occurs in COPD patients. In a healthy individual carbon dioxide receptors are responsible for 85% of drive to breathe, remaining 15% by oxygen receptors. In COPD patients, the carbon dioxide gets trapped in the alveoli and they cannot exhale it. According to Hoyt, this increase in carbon dioxide level cannot be solely attributed to the hypoxic drive. There are three important mechanisms explained.

- Haldane effect: This mechanism is associated with the haemoglobin (Hb), which has the ability to carry oxygen and carbon dioxide. When oxygen is administered to COPD patient, Hb carries the oxygen and its capacity to carry carbon dioxide will be reduced. Thus the plasma carbon dioxide level increases, COPD patient will not be able to exhale this carbon dioxide. (Williams et al., 2011)
- Hypoxic pulmonary vasoconstriction: This is a normal physiological response to the low levels of oxygen in alveoli. The pulmonary arteries constrict and allow the blood flow to oxygen deficient alveoli in healthy individuals. In COPD patients, as the oxygen is supplied, this pulmonary constriction does not occur causing an increase in carbon dioxide levels. (West, 2008)
- Reduced minute ventilation: Some COPD patients with acute respiratory failure reduce the minute ventilation due carbon dioxide retention and increase in the dead space ventilation. (Reilly et al., 2012)

Research evidence

In the above paragraphs, the theoretical evidence supporting the fact that oxygen administration does not remove the drive to breathe in COPD patients has been discussed. In this section, discussion of some of the research findings which prove that ‘restraining the oxygen therapy in COPD patients may do more harm than good’ will be addressed.

In a single blinded prospective study conducted at a medical-surgical intensive care unit of a tertiary teaching hospital, 12 intubated COPD patients with chronic carbon dioxide retention were observed at the baseline and after oxygen administration. There was no significant change in carbon dioxide levels, dead ventilation space and the respiratory drive. After the mechanical ventilation in these patients, the plasma levels of carbon dioxide were found to be lower and the minute ventilation was appropriate. (Crossley et al., 1997)

Dick et al. 1997 studied 11 hypoxemic COPD patients. The ventilator responses to hypercapnia and hypoxia were measured using evaluated rebreathing techniques. They have concluded that oxygen induced high carbon dioxide levels does not indicate any respiratory failure in all these 11 patients. Therefore it was proved that oxygen induced changes in the respiratory drive is not due to hypoxic drive in COPD patients. (Dick et al., 1997)

In a study conducted on 20 isocapnic hypoxic adults, the ventilator responses were recorded. The breathing pattern, respiratory drive and the minute ventilation were studied in these individuals. It was concluded that the minute ventilation may reduce; the partial pressure of carbon dioxide might increase when oxygen is given. (Easton et al., 1986)

A single blinded RCT conducted in the multidisciplinary intensive care units of a teaching hospital recruited the patients who were admitted with acute exacerbations of COPD with $PaO2 < 6.6kPa$. The patients were divided into two groups: one group receiving high oxygen tension (>9kPa) and the other low oxygen tension group (>6.6kPa). The effect of oxygen administration on the outcomes and the hypercapnia were studied in both groups. There was no patient with poorer outcomes in the high oxygen tension group, whereas one patient of low oxygen tension group received ventilation and other died. Thus this study noted that giving high levels of oxygen did not show any adverse effects on the patients. (Gomersall et al., 2002)

Aubier et al. 1980 studied the effects of giving 100% oxygen on the minute ventilation and levels of oxygen and carbon dioxide in patients with COPD with acute respiratory failure. When oxygen was administered there was an initial fall in respiratory volume, but after 15 minute of administration the minute ventilation improved which was very close to the control group. (Aubier et al., 1980)

A review published in 2010, focused on the long term oxygen therapy in the patients with acute exacerbations of COPD. It was shown that the survival rate was higher in patients who were given long term oxygen therapy (LTOT). The efficacy of LTOT was proved only in stable COPD patients with severe hypoxemia(<7.3kPa). (Corrado et al., 2010)

In a randomized controlled trial conducted on 27 patients, the effect of oxygen therapy on the quality of life of the patients with COPD was studied. It was shown that the oxygen improves the exercise performance in stable COPD patients. (Nonoyama et al., 2007)

In some studies it was shown that right proportion of oxygen administered to the COPD patients may save the life of the patient, without causing adverse effects of hypercapnia. The titrated oxygen administration to achieve 88-92% of oxygen saturation may result in reduced respiratory acidosis, decrease the mortality rate and also result in better outcomes. (Driscoll et al., 2008)

There are many evidences to suggest that the benefits of long term oxygen therapy are numerous and even the mortality rate has been significantly decreased. Thus, long term oxygen therapy increases the survival rates in COPD patients with acute exacerbations. (BTS, 2015)

METHODOLOGY

Literature search

A search including all the articles in English from the search engines such as PUBMED, MEDLINE, CINAHL Plus, COCHRANE database was done. The initial search included all the articles available from all the sources. A secondary search of articles from the in text citations of the primary articles was performed. The important key words used in search strategy are COPD patients, oxygen therapy, hypoxic drive, respiratory drive, ventilation.

Inclusion and Exclusion criteria

The articles addressing the outcomes of oxygen therapy in the COPD patients were included. We included all the study designs including observational, RCTs, cohort studies, etc. The articles with no information of number of patients studied, outcomes, adverse effects were excluded from this review.

Quality of literature

The quality of the included literature has to be assessed in order to get the genuine results of the review. Different scales used for the assessment of the quality are Jadad scale, Structured Effectiveness Quality Evaluation Scale (SEQES) and Sackett's Level of Evidence.

DATA ANALYSIS

As this review includes different studies with variations in sample size, settings, study designs, outcomes measured, heterogeneity is a matter of concern. Hence appropriate statistical tests such as ANOVA and chi-square tests will be used in the final review process. In addition, forest plots can be constructed to get a clear view of the result as the research question is a debate or controversial in nature.

SIGNIFICANCE

Since decades there has been a debate over the topic if the oxygen can be given to the patients with COPD or not. This review was proposed in order to study the evidences which show the beneficial effects of oxygen therapy in patients with acute exacerbations of COPD. The much debated hypoxic drive theory has been proved wrong by the evidences in past as patients do not die of respiratory failure due to high oxygen levels after the administration. The theories like Haldane effect, minute ventilation and pulmonary constriction were implicated for the hypoxic drive. Hence, restraining the oxygen therapy in COPD patients when required may pose more hazards than the benefits. It is because hypoxia kills, whereas hypercapnia occurs. Hence, care should be taken by the medical and the nursing professionals to focus on how to treat hypercapnia instead of letting the patient die of hypoxia. This review is in the proposal phase, hence it needs to be supplemented by different data analysis techniques and statistical tools to get the quantitative conclusions.

REFERENCES

Aubier M, et al. (1980). Effects of the administration of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis*, 122, 747-754.

British Thoracic Society and BTS Home Oxygen Guideline Group. (2015). BTS Guidelines for Home Oxygen Use in Adults;

Corrado, A., Renda, T., & Bertini, S. (2010). Long-term oxygen therapy in COPD: evidences and open questions of current indications. [Review]. *Monaldi Arch Chest Dis, 73*(1), 34-43.

Crossley DJ, McGuire GP, Barrow PM, Houston PL. (1997).Influence of inspired oxygen concentration on deadspace, respiratory drive, and PacO2 in intubated patients with chronic obstructive pulmonary disease. *Crit Care Med*, 25(9), 1522-1526.

Easton PA, Slykerman LJ, Anthonisen NR. (1986). Ventilatory response to sustained hypoxia in normal adults. *J Appl Physiol*, 61, 906-911

Gomersall, Charles D., et al. (2002). Oxygen Therapy for hypercapnic patients with chronic obstructive pulmonary disease and acute respiratory failure: A randomized, controlled pilot study. *Crit Care Med*, 30(1), 113-116

Hoyt JW. (1997). Debunking myths of chronic obstructive pulmonary disease. *Crit Care Med*, 25,1450-1451.

Kent BD, Mitchell PD, McNicholas WT. (2011). Hypoxemia in patients with COPD: cause, effects, and disease progression. *Int J Chron Obstruct Pulmon Dis*, 6(1), 199-208.

Nonoyama, M. L., Brooks, D., Guyatt, G. H., & Goldstein, R. S. (2007). Effect of oxygen on health quality of life in patients with chronic obstructive pulmonary disease with transient exertional hypoxemia. [Randomized Controlled Trial

Research Support, Non-U S Gov't]. *Am J Respir Crit Care Med, 176*(4), 343-349.

O'Driscoll BR, Howard LS, Davison AG. (2008). BTS guideline for emergency oxygen use in adult patients. *Thorax*,63 (Suppl 6), 1-68.

Reilly JJ, Silverman EK, Shapiro SD. (2012). *Chronic obstructive pulmonary disease*. In Fauci AS, Kasper DL, Jameson JL, et al. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012

West JB. (2008). *Respiratory Physiology: The Essentials*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

Williams DM, Bourdet SV. (2011). *Chronic obstructive pulmonary disease*. In: Talber RL, DiPiro JT, Matzke GR, et al. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York, NY: McGraw-Hill; 2011.