Research Study Protocol

Title

Effect of High-Flow Nasal Cannula (HFNC) on the Breathlessness, Cough, and Sputum Scale (BCSS), in patients with stable Chronic Obstructive Pulmonary Disease (COPD)

Investigators

Principal investigator: Karen Allen, M.D
Co-investigator: Tony Abdo, M.D
Affiliation: The University of Oklahoma Health Sciences Center; Department of Medicine; Division of Pulmonary, Critical Care, and Sleep Medicine.

Sponsor

High Flow Nasal Cannula Devices will be donated by Fisher & Paykel Healthcare, Inc.

Introduction and Background

Over the last few years, High Flow Nasal Cannula (HFNC) has been gaining a lot of popularity in adult population. High Flow Nasal Cannula oxygen therapy consist of an air/oxygen blender, an active humidifier, a single heated circuit, and a nasal cannula. It has the potential to deliver a flow rate up to 60L/min in adults and an inspiratory fraction of oxygen (FiO2) close to 100%[1,2]. Multiple mechanisms have been suggested to contribute to the clinical benefit of HFNC, including and not limited to[1, 2]:

- The use of small loose-fitting nasal prongs leads to enhanced patient comfort
- Heat and humidification increase water content of mucus, facilitating secretions removal, minimizing desiccation/epithelial injury, and decreasing metabolic cost/work of breathing;
- Higher nasal flow rate provides a more reliable FiO2 delivery by reducing inspiratory entrainment of room air
- Washout of upper airway dead space improves efficiency of ventilation and enhances oxygen delivery
- Generation of a positive end-expiratory pressure (PEEP) counterbalances auto-PEEP and decreases work of breathing

The use of HFNC has been limited to the inpatient setting, and mostly to intermediate care (step down) and intensive care units. It has been predominantly used in mild to moderate hypoxemic respiratory failure to delay and hopefully prevent endotracheal intubation and mechanical ventilation. A recent large, randomized, multicenter trial showed that in hypoxemic non-hypercapnic respiratory failure, HFNC has similar intubation rate to non-invasive positive pressure ventilation (NIPPV), but a lower 90 days mortality[3]. On the other hand, the data on

HFNC use in other settings is lacking and is limited to anecdotal cases and small pilot studies. Despite this lack of strong data, HFNC has been frequently used in a variety of patients with different diseases. It has been used in acute pulmonary edema, in immunocompromised and Do-Not-Intubate patients, pre-intubation, post-extubation, during endoscopy, in sleep apnea, and even in acute COPD exacerbation[1, 2].

Data on HFNC use in patients with COPD include the following:

- In a small recent study including patients with stable COPD and moderate hypercapnia (PaCO2 ~ 53mmHg), six weeks of HFNC caused a significant drop in PaCO2 (~ 8 mmHg), comparable to the drop observed with NIPPV [4].
- A small pilot study looked into effects of eight hours of HFNC on ventilation in healthy volunteers, COPD, and idiopathic pulmonary fibrosis patients. In patients with stable COPD, an increase in tidal volume (VT) was noted with a drop in PaCO2, despite a drop in respiratory rate (RR) and minute ventilation (MV) [5].
- In another small pilot study, 45 min of HFNC at 20L/min on RA, lead as well to a decrease in respiratory rate and no significant change in PaCO2 [6].

This suggests that HFNC increases the efficiency of breathing/ventilation. HFNC generates low levels of positive end-expiratory pressure (PEEP) which is known to decrease ventilation/perfusion mismatch. Low levels of PEEP may contribute as well to alveolar recruitment and decrease dead space/tidal volume (VD/VT) ratio. Through delivering a higher flow, HFNC may be contributing to the washout of upper airway dead space as well.

Based on the proposed mechanism of actions, the physiologic effects of HFNC (loosening up secretions, washing out dead space, and generating a CPAP/PEEP effect), and the data from previous pilot studies showing an improvement in respiratory efficiency with HFNC; we postulate that the use of HFNC in patients with stable COPD in the outpatient setting is safe, and may result in BCSS [7] score reduction, better quality of life, and possibly fewer exacerbations.

What distinguishes our study is, that to the best of our knowledge, it is the first one where HFNC effectiveness will be studied in COPD patients in the outpatient setting, and for a relatively longer period of time. A positive outcome may open the door for a larger randomized controlled study, which if it validates this outcome, may provide patients with COPD an effective non-invasive alternative home device.

Objectives

The primary objective of this study is to look for a correlation between the use of HFNC in the outpatient setting in patients with previous COPD exacerbation and the change in their BCSS score. We hypothesize that home use of HFNC will lead to a reduction in BCSS score by 1.3.

Secondary objectives include; looking for a correlation between the use of home HFNC and COPD exacerbations in a 6 month period. COPD exacerbations are defined as worsening symptoms of COPD requiring a change in baseline medications/inhalers or a steroid or antibiotic prescription. No arterial blood gases will be performed as part of the study but we will look for PaCO2/serum bicarbonate change with the use of home HFNC, when possible.

Study Design and Methodology

This is a prospective pilot study. Targeted population include patients with COPD, non-oxygen dependent, with a baseline normal bicarbonate on previous lab (within 6 months of enrollment). Patients will be randomly selected to be part of the study sample. Recruitment will occur in both inpatient and outpatient settings. An email briefly explaining the objectives of the study will be sent to Internal Medicine residents and Pulmonary Critical Care fellows to help in patients' recruitment. Patients will be enrolled in the study only after being seen by Dr. Abdo or Dr. Allen. The study is expected to finish by the end of January 2017 or twelve months post IRB approval. Patients will be recruited and enrolled over six months, and the collected data will be analyzed six months after the last patient was included in the study. We will target a study sample of 30 as detailed in the statistical analysis section, where patients will be their own control (3 months without HFNC followed by 3 months with HFNC).

At the time of enrollment, demographic data, forced expiratory volume (FEV1) and a baseline PaCO2/serum bicarbonate when available will be collected. Patients will be taught how to calculate the BCSS score and will be provided with 120 photocopies of the BCSS score table (Table.1). They will be asked to complete the BCSS score every night if possible or at least 3 times per week. Patients will be followed for a total of 3 months, prior to starting home HFNC. Patients who were enrolled post COPD exacerbation will be followed for an extra month (a total of 4 months) and their BCSS scores from the first month will not be included in the statistical analysis since they will not be at their baseline at the time of enrollment. Compliance to follow up visits and completing the BCSS score will be a requirement to qualify for starting HFNC. To improve compliance, a follow up in the clinic or over the phone will take place at 6-8 weeks post enrollment.

After 3-4 months follow-up post enrollment, patients will be brought to the clinic for HFNC education/fitting. A baseline BCSS score ($BCSS_0$) will be completed and the mean of last 3 months' BCSS scores ($\overline{BCSS}_{\text{w/oHFNC}}$) will be calculated. The number of COPD exacerbation per last 3 months with new baseline PaCO2/serum bicarbonate, if available, will be collected. The HFNC device will be set at a fixed flow of 30L/min and a FiO2 of 21% (room air). Patients will be instructed to wear HFNC as long as they can while targeting at least 6 hours/day, and to record the number of hours they wear it per day. Patients will continue to complete the BCSS score every night or at least 3 times per week. After 6-8 weeks, a follow-up appointment over the phone or in the clinic will take place.

At the end of the 3 months HFNC trial, patients will be brought back to the clinic, and a BCSS score will be completed ($BCSS_3$) and the mean BCSS of the last 3 months ($\overline{BCSS}_{\text{w/HFNC}}$) will be calculated. The number of hours/day wearing the HFNC, the number of COPD exacerbations per last 3 months, and new baseline PaCO2/serum bicarbonate (if available), will be collected.

Both the difference between the mean of baseline BCSS scores ($\overline{BCSS}_0$) and the mean of BCSS scores post 3 months HFNC ($\overline{BCSS}_3$), ($\Delta 0\text{-}3\ \overline{BCSS}$); and the difference between the means of the means of BCSS without HFNC ($\mu_{\overline{BCSS}_{\text{w/oHFNC}}}$) and with HFNC ($\mu_{\overline{BCSS}_{\text{w/HFNC}}}$), ($\Delta\ \mu_{\overline{BCSS}_{\text{w/oHFNC}}} - \mu_{\overline{BCSS}_{\text{w/HFNC}}}$) will be calculated. The difference between the means of number of COPD

exacerbation per 3 months pre and post-HFNC, and the means of baseline PaCO2/serum bicarbonate (if available) pre and post-HFNC will be calculated as well, as secondary objectives. We will also look for a possible correlation between the number of hours using home HFNC and the change in BCSS score.

Regardless of the change/or not in BCSS score, patients will be able to provide their feedback regarding the device; they will be asked how helpful it was on a scale of 0 to 3, with 0 being equivalent to "not helpful at all" and 3 corresponding to "very helpful". Patients will be asked as well if they would like to keep/not keep the device.

Eligibility Criteria

All patients aged between the ages of 35 and 80 years old, in the inpatient and outpatient settings, carrying a diagnosis of COPD, confirmed by spirometry, with at least one COPD exacerbation in the past year, non-oxygen dependent, and having a baseline PaCO2 < 60 mmHg/or normal serum bicarbonate within the last 6 months are eligible for enrollment.

Patients will be excluded from the study if they fail to sign an informed consent, do not meet the inclusion criteria, remain oxygen dependent post COPD exacerbation, and do not meet the basic mental, physical, and educational capabilities to complete the BCSS score.

Statistical Analysis

Based on the "Breathlessness, Cough, and Sputum Scale" study in CHEST[7], a reduction in BCSS score of 1.3 with a standard deviation of 1.8 is correlated with a highly efficacious treatment.
For this study to have a 90% power (β) to detect a difference in the population means (δ) of 1.3 with a standard deviation of difference in the response of matched pairs (σ) of 1.8, and using a paired t-test with an α of 5%, we are required to enroll 22 patients. Assuming a 25% drop rate throughout the study period, we need to aim for a sample size of 30 patients.

Risks and Side Effects:

No major risks or side effects are expected during the study since no invasive interventions will be performed. Infrequently, patients may develop a localized facial trauma and erythema at pressure areas, discomfort, and epistaxis.

Data management and Safety Monitoring Plan

All the data will be recorded anonymously using study subject number rather than personal identifiers. There will be one password protected master list kept on an encrypted computer with patient's name and DOB correlating with study subject number. This computer will be secured in a locked office in the section of pulmonary and critical care office.

OUHSC regulations regarding electronic information and data security will be followed. If an incident such as loss or theft of data or storage media, unauthorized access of sensitive data or devices, or non-compliance with security controls occurs, the PI will be notified and will report the data security incident to OUHSC authorities.

Informed consent:

Informed consent form available in English will be provided to patients to sign. Patients will receive an appropriate explanation about the study, and they will be given the opportunity to ask questions and have their questions answered.

References

1. Spoletini G, Hill NS, et al. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. *Chest. 2015 Jul;148(1):253-61*
2. Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care. 2015 Mar 31; 3(1):15.*
3. Frat JP, Robert R et al.; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med. 2015 Jun 4;372(23):2185-96*
4. Bräunlich J, Wirtz H, et al. Nasal High-flow versus non-invasive ventilation in stable hypercapnic COPD: a preliminary report. *Multidiscip Respir Med. 2015 Sep 3;10(1):27*
5. Bräunlich J, Wirtz H, et al. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. *Respiration. 2013; 85(4):319-25.*
6. Nilius G, Schneider H, et al. Effects of nasal insufflation on arterial gas exchange and breathing pattern in patients with chronic obstructive pulmonary disease and hypercapnic respiratory failure. *Adv Exp Med Biol. 2013; 755:27-34.*
7. Leidy NK, Goldman M, et al. The breathlessness, cough, and sputum scale: the development of empirically based guidelines for interpretation. *Chest. 2003 Dec; 124(6):2182-91.*

Appendix

Table1. The Breathlessness, Cough, and Sputum Scale (BCSS)

Permission to use this score obtained from Dr. Mitchell Goldman (mitchell.goldman@astrazeneca.com)

Please complete in the evening (prior to going to bed)
Please enter day (Monday, Tuesday, etc.):
Please record the date (day/month):
How much difficulty did you have breathing today? ▪ 0 = None: unaware of any difficulty ▪ 1 = Mild: noticeable during strenuous activity (*eg*, running) ▪ 2 = Moderate: noticeable during light activity (*eg*, bedmaking) ▪ 3 = Marked: noticeable when washing or dressing ▪ 4 = Severe: almost constant, present even when resting
How was your cough today? ▪ 0 = None: unaware of coughing ▪ 1 = Rare: cough now and then ▪ 2 = Occasional: less than hourly ▪ 3 = Frequent: one or more times an hour ▪ 4 = Almost constant: never free of cough or need to cough
How much trouble was your sputum today? ▪ 0 = None: unaware of any difficulty ▪ 1 = Mild: rarely caused problem ▪ 2 = Moderate: noticeable as a problem ▪ 3 = Marked: caused a great deal of inconvenience ▪ 4 = Severe: an almost constant problem
Total Score: