

Nebulized Hypertonic Saline for Inpatient Use in Chronic Obstructive Pulmonary Disease

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Introduction

Chronic obstructive pulmonary disease (COPD) continues to be a significant contributor to morbidity and mortality with significant resources allocated for inpatient COPD exacerbations^{1,2,3,4}, defined on clinical symptoms of increased cough from baseline, a change in sputum characteristics from baseline (color, consistency, volume), or increase in the patient's dyspnea from baseline^{5,6,7}. Current guidelines for treating exacerbations of COPD utilize steroids for reducing inflammation, supplemental oxygen for hypoxemia, antibiotics if suspicion is for a bacterial cause of the exacerbation, and bronchodilators for symptom control and improving airflow per the guidelines published by the Global Initiative for Chronic Obstructive Lung Disease⁸. Additionally, counseling on cessation of cigarette smoking should be given to those still smoking. Supportive therapy with mechanical ventilation (invasive or non-invasive) may be necessary as well as fluid balance management, nutrition, and vaccinations as appropriate for Pneumococcal pneumonia and seasonal influenza. Symptomatic treatment may include pulmonary hygiene with chest physiotherapy such as by a respiratory therapist/percussion vest/Acapella or flutter valve device, and mucolytics such as guaifenesin or N-acetylcysteine (NAC) (as mucolytic or antioxidant)⁸.

Although mucolytic therapy is mainly symptomatic and long-term studies are not definitive, some patients may have benefit^{9,10,11,12,13}. Additionally, NAC may have benefit in COPD exacerbations^{14,15,16,17}. However, with the recent drug shortages, NAC is not readily available in many hospitals. With difficulty in obtaining a potentially beneficial medication and with significant costs, it is beneficial to explore other possibilities that may deliver equal or better options.

Nebulized hypertonic (3%) saline has been used for sputum induction and as a mucolytic, mainly in pediatric populations with bronchiolitis, and in cystic fibrosis patients with bronchiectasis^{18,19,20}. Potential benefits of nebulized hypertonic saline include its availability and its costs. Its packaging includes both individual respules for nebulization and bulk solutions.

Methods

Study Population:

This study will involve 146 patients admitted to Doctors Hospital in Columbus, Ohio from September 2014 through September 2015 with a clinical diagnosis of an acute exacerbation of COPD, defined as an increase in the patient's dyspnea, cough, or change in sputum consistency/volume/color from the patient's baseline during stable conditions. To achieve 80% power to detect a clinically significant difference between study groups, a minimum sample size of 130 patients (65 in each study group) is necessary. To account for issues such as patient study withdrawal and protocol deviations, a sample size of 146 patients (73 per study group) is ideal.

Inclusion Criteria:

- Patients at least 18 years of age
- Admitted to Doctors Hospital with a clinical diagnosis of COPD within 24 hours.

Exclusion Criteria:

- Patients younger than 18 years of age
- History of smoking less than twenty pack-years
- Possibility of other primary cause of the patient's change in dyspnea or cough (e.g. pneumonia, congestive heart failure with pulmonary edema, myocardial infarction)
- Patient is found to have a different primary cause after initial enrollment
- Patients admitted over 24 hours prior to contact by study staff/investigator
- Non-English speaking subjects

Hypothesis:

A clinically significant difference exists between albuterol treatments with nebulized 3% saline versus standard saline, for improvements in the patient's modified Borg dyspnea score during an acute exacerbation of COPD.

Study Design:

This randomized, single-blind, prospective study will involve 146 patients admitted to Doctors Hospital with a clinical diagnosis of an acute exacerbation of COPD. Patients will be randomly assigned to 2.5 mg albuterol treatments with either normal saline, as is the standard, or hypertonic saline. The Doctors Hospital biostatistician will create a randomization plan that will be kept with the consent forms. The investigator or study staff will maintain the list and determine the study treatment by subject number.

Once the patient has been identified by the inclusion/exclusion criteria, they will be approached by a study staff member and informed of the opportunity to participate in the study. The study staff will then provide a detailed explanation of the study and obtain patient consent.

Once the patient is enrolled, they will receive the 2.5mg albuterol treatment, and saline solution as determined by the randomization plan (Group 1 will receive 0.9% saline and Group 2 will receive 3% saline), every six hours for at least the first 24 hours, with allowance for PRN (*pro re nata*= as needed) use every four hours by patient request. The nebulized saline will be kept in the pharmacy and will be ordered in the same way as the standard saline. The patient's dyspnea will be evaluated prior to starting the treatment and after the intervention period is completed using the Modified Borg Dyspnea Scale²¹. The scale will be administered by either the investigator or study staff.

Participation in the study will be complete once the patient is discharged from the hospital. All patients will be recommended to have spirometry or full pulmonary function testing as an outpatient once stable, if not already obtained.

Data Storage and Confidentiality

Only de-identified or non-identifiable data will be reported in the study. Only the research investigators and study staff will have access to patient information. All resulting data will be stored in electronic format; files will be stored on a password-protected computer and stored in a secured facility with limited access. Participants will not be excluded on socioeconomic, racial or religious identity. No form of deception will be used. The data collection and storage processes will follow HIPAA guidelines, in accordance with 21 CFR 46.115 (b); to protect both confidentiality and privacy of each participant. All PHI data will be erased or destroyed per institution protocol.

Study Variables:

The data to be collected from this study will include:

- Demographic (age, sex)
- Treatment group (normal saline/hypertonic saline)
- Modified Borg Scale Score (pre and post treatment)
- prn albuterol use
- 30 day readmission
- 30 day all cause mortality
- Spirometry data within 30 days

Statistical Analysis:

We will test the hypothesis that a clinically significant difference in dyspnea scores exists between patients who receive hypertonic saline and those who do not. Descriptive statistics will be produced, using means, medians, ranges and standard deviations for continuous variables, and percentages for categorical variables. Independent variables will include modified Borg scores, 30-day mortality and length of hospital stay. Inferential statistics will determine statistically significant differences between comparison variables, using paired sample t-tests or the Wilcoxon signed rank test. Statistical significance will be evaluated at the 5% ($\alpha=0.05$) level.

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