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Research Proposal for Review
Seton Institutional Review Board

I. Title

Comparison of Breath-Enhanced and T-Piece Nebulizers in Children with Acute Asthma

II. Investigators (co-investigators), Study Team Members, and Institutional Affiliations

Principal Investigator:

Matthew Wilkinson, MD
The University of Texas at Austin, Dell Medical School
Dell Children's Medical Center of Central Texas
Austin, TX

Co-Investigators:

Michael Gardiner, MD
The University of Texas at Austin, Dell Medical School
Dell Children's Medical Center of Central Texas
Austin, TX

III. Source of Funding

This study has received funding from the 2014 Scientific, Education and Research Foundation of UTSW Austin Research/Fellow Grant (SERF-RG) in the amount of $4997 to cover equipment and gift cards for patient enrollment incentive.

The Dell Children's Medical Center Pediatric Emergency Medicine Fellowship will fund any further expenses incurred.

IV. Hypothesis, Research Questions, or Goals of the Project

The objective of this study is to evaluate the efficacy of two different nebulizers. We hypothesize that albuterol delivered with a breath-enhanced nebulizer will lead to statistically greater improvement in FEV_1 when compared to an equivalent dose delivered via a standard t-piece nebulizer. The primary aim will be to study changes in forced expiratory volume in one second (FEV_1) in patients presenting to an urban pediatric emergency department with a moderate to severe acute asthma exacerbation when utilizing these two nebulizers. Secondary aims will include evaluation of hospital admission rates, emergency department (ED) length of stay (LOS), changes in asthma severity scores, vital sign changes, medication side effects, and total quantity of albuterol given in the ED. A distal aim of the study will be to perform a cost analysis; though we will likely need further clinical trials utilizing multiple dose administration in order to accurately analyze cost.

V. Background and Significance

Acute asthma exacerbation is one of the most frequent reasons for children to visit the emergency department. According to the 2011 Centers for Disease Control and Prevention National Health Interview Survey, there are 7.1 million children living with a diagnosis of

asthma.[1] Among the surveyed children, 58% had at least one asthma attack within the prior year.[1] In 2010, 640,000 children under 15 years old visited an emergency department for asthma related reasons.[1] The treatment of asthma accounts for a large portion of our national healthcare expense with an estimated annual cost of $56 billion, of which children account for a significant portion.[1]

Advances in the ability to safely, effectively, and efficiently treat asthma exacerbations have the potential to improve outcomes, patient flow, and the productivity of pediatric emergency departments. Current standard of care treatment of acute asthma includes administration of an inhaled short acting β_2-agonist (SABA), systemic glucocorticoids, and correction of hypoxemia.[2] While it has long been accepted that the use of inhaled SABA is efficacious, the optimal route of administration has been controversial. Despite several studies showing that metered dose inhalers (MDI) with spacer are likely as effective as nebulizers, ED physicians in the United States have been reluctant to change their practice.[3-8]

Fueled by the ongoing investigation into the ideal mechanism of inhaled SABA delivery, nebulizer technology has continued to advance over the past several decades. Studies using in-vitro lung models and in-vivo healthy controls have shown newer nebulizer technologies to aerosolize more medication with droplet sizes in the ideal respirable range, increasing the efficiency of drug delivery and improving lung deposition.[9-14] It is unknown whether these results will translate into improved clinical outcomes.

Newer generation nebulizers include breath-actuated and breath-enhanced nebulizers. Breath-actuated nebulizers function via a piston-activation, which initiates nebulization only during patient inhalation, enhancing medication delivery and reducing waste. The drawbacks of breath-actuated nebulizers include their high cost, significantly longer nebulization times, and occasional non-activation when a patient is unable to generate significant inspiratory force to initiate nebulization, which is a significant problem in the pediatric population.[14,15] Breath-enhanced nebulizers, on the other hand, continuously nebulize medication and gain their advantage via an aerosol holding chamber and a one-way valve system that directs exhaled air away from the nebulizer chamber. This technology minimizes medication loss upon exhalation, and allows nebulized aerosol to build up in the chamber prior to the next breath cycle, thus delivering a bolus dose of medication on inhalation.[12-14]

Newer technology nebulizers have not been widely accepted into clinical practice largely due to healthcare comfort with existing practices, lack of clinical trials evaluating efficacy in sick patients, and concerns regarding the cost of these newer nebulizers. Despite the benefits that have been demonstrated in healthy subjects and lung models, few studies have evaluated these newer technology nebulizers in pediatric patients presenting with acute asthma exacerbations. One randomized controlled trial of pediatric patients demonstrated decreased symptom scores, respiratory rates, and lower admission rates with the use of breath-actuated nebulizers compared to t-piece nebulizers.[15] We were only able to identify one study which analyzed spirometry data in pediatric patients with newer nebulizer technologies.[16] In this study, patients receiving inhaled terbutaline showed greater FEV_1 improvement using a breath-actuated device as compared to a constant flow nebulizer.

To our knowledge, the efficacy of breath-enhanced compared to t-piece nebulizers on airway obstruction as determined by spirometry has not been evaluated in children with acute asthma. There is an ongoing study at our institution (principal investigator is Dr. Wilkinson) that is evaluating ED LOS in pediatric asthma patients when placed on a breath-enhanced versus t-piece nebulizer treatment pathway. Dr. Wilkinson's study is not evaluating FEV_1 or other spirometric data to measure airway obstruction or the efficacy of a single treatment. Measurement of FEV_1 has been used throughout other asthma literature as a reliable measure of airway obstruction and effectiveness of treatment in patients with acute asthma.[16-19] FEV_1 measurement has been recommended by the National Heart, Lung, and Blood Institute (NHLBI) as a means of assessing the degree of airway obstruction, and response to therapy in acute asthma.[2] In their 2007 guidelines, the NHLBI recommended routine FEV_1 measurements in all patients presenting for acute asthma exacerbations, as this measure is a more reliable indicator of severity of exacerbations than severity of symptoms.[2] Additionally, FEV_1 is more useful than peak expiratory flow (PEF) due to the ability to evaluate flow-volume loops and distinguish poor effort and restrictive lung diseases from asthma-related obstruction.[20-22] For all of these reasons, we feel it is pertinent to study this breath-enhanced nebulizer technology in relation to clinical spirometric data in order to demonstrate clinical efficacy.

VI. Research Method, Design, and Proposed Statistical Analysis

This study will be a blinded observer, randomized, controlled trial comparing breath-enhanced nebulizer albuterol therapy with nebulized albuterol administered via a t-piece nebulizer.

The study site will be the Dell Children's Medical Center Emergency Department, an urban pediatric ED with approximately 80,000 visits per year, of which than 3000 visits are due to asthma related issues. The patient population will include children with previously diagnosed asthma, aged ≥ 6 years to < 18 years old, presenting to our pediatric ED with breathing difficulty or cough, and found to have an initial FEV_1 less than 70% predicted based on NHANES III study data (moderate to severe exacerbation). [2,15,23] Patients will be excluded from the study if they have no clinical evidence of exacerbation by asthma scoring (PAS score of 0), have preexisting chronic lung disease besides asthma, have congenital heart disease, have neuromuscular disease, have a suspected intrathoracic foreign body, have an allergy or other contraindication to a study medication, or have severe breathing difficulty requiring immediate resuscitation.

<u>Subject Eligibility:</u>
Inclusion:

1. Age ≥ 6 years and < 18 years
2. History of physician diagnosed asthma
3. Presenting to ED with acute asthma exacerbation
4. Parent or guardian speaks English or Spanish.

Exclusion:

1. PAS score of 0
2. Initial FEV_1 greater than 70% predicted
3. Patient unable to perform acceptable initial spirometry
4. Pregnancy or breast-feeding
5. Immediate resuscitation required
6. Chronic lung disease (other than asthma)
7. Congenital heart disease
8. Neuromuscular disease
9. Suspected intrathoracic foreign body
10. Allergy or other contraindication to study medication

Subjects will be identified in triage and will be screened and enrolled by a member of the study team (P1). A research nurse will be available for 6-8 hours per day to serve as the primary enrolling personnel during these hours. Additionally, each of the pediatric emergency medicine fellows and several pediatric emergency medicine attending physicians will be trained and certified for enrollment, and will enroll subjects during evenings, nights, and weekends. We anticipate having study personnel available at a minimum of 18 hours per day for enrollment. The P1 personnel will assess the potential subject and screen potential subjects for inclusion and exclusion criteria as detailed above. As a part of screening, the P1 personnel will perform baseline spirometry measurements prior to consent. Spirometry is a minimal risk procedure that is performed as standard of care in many emergency departments nationwide (either as spirometry, or PEF measurements). Performing spirometry prior to consent will expedite screening, and for children who have FEV_1 greater than 70% predicted or those unable to perform acceptable spirometry, this will allow them to be excluded and their asthma treated more promptly. This will avoid excluded children having to undergo consent prior to being excluded and receiving treatment for their acute asthma. Consent will be obtained from the parent or guardian of all patients, and assent obtained from patients who are at least 7 years of age. If required prior to study enrollment, supplemental oxygen may be administered to maintain oxygen saturation > 90% if there is evidence of hypoxemia on continuous pulse-oximetry. If there is a delay of greater than 15 minutes due to the consent process, a unit dose (2.5mg) of albuterol may be given with a standard t-piece nebulizer up to 3 times as needed. Patients requiring this unit dose of albuterol will still be eligible for enrollment so long as they meet enrollment criteria following this therapy. Following consent, the P1 personnel will record an initial set of vital signs (temperature, heart rate, respiratory rate, blood pressure, and peripheral pulse oximetry), and record baseline asthma scores using multiple previously validated asthma severity scores (PAS and PASS).[24,25] At this point, study patients will be randomized to receive treatment with either the experimental (breath-enhanced) or control (t-piece) nebulizer. Randomization will be performed with a computerized randomization process. Pre-assigned opaque envelopes will be used in order to conceal randomized assignments, preventing any knowledge of patient assignment to the enrolling personnel. A second

member of the study team (P2) will open the subject's randomized folder that will dictate the appropriate therapy arm. P2 will administer a single 5mg dose of albuterol via the appropriate nebulizer as determined by randomization. P1 will be blinded to the treatment arm, whereas P2 will not be blinded. Following 15 minutes of therapy - sufficient time for both treatment arms to be complete - P1 will perform a post-treatment assessment of the subject including a repeat set of vital signs, pulse-oximetry, asthma scoring, and spirometry measurements.

Patients randomized to the "control" arm will receive therapy with our standard ED nebulizer, the Hudson RCI® Micro Mist® nebulizer (Teleflex Medical®, Research Triangle Park, NJ). The treatment will be preferentially administered with a mouthpiece. Patients unable or unwilling to use a mouthpiece (as determined by the P2) will receive therapy with a simple mask (Hudson RCI®, Teleflex Medical®, Research Triangle Park, NJ).

Patients randomized to the "experimental" arm will receive therapy with a NebuTech® HDN®, Breath-Enhanced High Density Jet Nebulizer (Salter Labs®, Arvin, CA). Treatments will be preferentially administered with a mouthpiece. Patients unable or unwilling to use a mouthpiece (as determined by the P2) will receive therapy with a mask. The NebuTech® HDN® allows for a proprietary vented mask, which still utilizes the breath-enhanced features of the system (I-Guard™ Valved Aerosol Delivery System, Salter Labs®, Arvin, CA).

Spirometry measurements will be taken using a handheld spirometer which has been validated in healthy controls (NDD EasyOne®).[26] In keeping with the most recent American Thoracic Society guidelines, participants will asked to perform a minimum of 3 and maximum of 8 forced expiratory maneuvers in order to obtain 3 adequate samples as determined by the device.[27] Based on prior data, more than 8 attempts at spirometry may result in patient fatigue which will artificially decrease the patient's performance on lung function testing[27]. The highest recorded FEV_1 will be used for analysis. Flow-volume loops will be evaluated by a pulmonologist in order to assess adequacy of spirometry measurements for all patients, and those with inadequate loops will be excluded from FEV_1 analysis. The pulmonologist involved will be blinded to therapy arm.

A member of the research team will collect baseline data from the subject's guardian. Data will be recorded on a standardized form and will include subject demographics (including age, ethnicity, primary care provider), baseline home therapies, and assessment of baseline asthma severity, nature and duration of current symptoms, and treatments prior to ED arrival. Following the post-treatment assessment, the P1 (blinded) study personnel will be asked to predict which nebulizer was utilized in the study, in order to evaluate adequacy of blinding.

Following completion of the experimental stage as detailed above, patients will be released to receive standard of care therapy as determined by the assigned attending ED physician. We anticipate that the majority of patients will receive care according to the DCMC ED asthma pathway, including administration of inhaled ipratropium bromide and an oral systemic glucocorticoid. However, some patients may be treated off of the ED pathway, and variability in subsequent therapy is possible. Data will be recorded on a standardized form

regarding subsequent therapy through the remainder of the patients' ED course. Patients who are admitted to the hospital will be treated according to the standard of care as determined by the inpatient attending physician. Following disposition from the ED, no further data will be obtained from patients.

Sample Size

Treatment groups will be analyzed on an intention-to-treat basis. The primary outcome for this study is change in FEV_1 from initial presentation to reassessment. By evaluating data from previously performed studies,[16,18] we have conducted a sample size calculation using an estimated baseline initial FEV_1 of 55% predicted, and an estimated 10% FEV_1 improvement with standard of care. The calculations were performed using STATA 13 statistical software (StataCorp, LP, College Station, TX). In order to detect an improvement differential of 5% (absolute) between treatment arms, with a power of 0.80 and alpha of 0.05, we will need 64 patients enrolled in each arm. It has been shown previously that as few as 35%-65% of patients with severe asthma exacerbations are able to successfully perform peak expiratory flow or spirometry.[22,28] However other studies have not had significant difficulty with pediatric subjects performing spirometry.[15] Several of these studies evaluated patients as young as 5 years old. Due to the inconsistency of data, and the fact that we will be enrolling patients 6 years and older, we estimate that with sufficient coaching, approximately 60% of patients in this study will be able to successfully complete interpretable spirometry. Based on this, we will need to enroll 213 patients in order to obtain interpretable data on 128 patients. We will perform ongoing flow-volume loop analysis of obtained data in order to adjust our total enrollment goal based on the percentage of subjects with interpretable data sets.

Statistical Analysis

The primary outcome of change in FEV_1 will be compared between the two groups using a two-tailed t-test, or non-parametric equivalent if the data is non-normally distributed. Baseline group characteristics will be summarized in a table with means and standard deviations for continuous data, percentages for categorical data, and medians with interquartile ranges for ordinal data.

Secondary outcomes for this study will include hospital admission rates, emergency department (ED) length of stay (LOS), changes in asthma severity scores, vital sign changes, medication side effects, and total quantity of albuterol given in the ED. Analysis of these variables will be completed using appropriate statistical analysis depending on the nature of the data (t-test for continuous, chi square of Fisher's exact test for categorical, and Mann-Whitney U test for ordinal). Non-parametric tests will be used when appropriate.

Finally, if significant baseline differences in the groups occur, linear multivariable regression analysis of the primary endpoint will be performed to adjust for potential confounders.

VII. Human Subject Interactions

a. Sources of Potential Participants

Subjects will be screened for enrolment if they present to the DCMC ED with signs of an acute asthma exacerbation. The nursing staff at triage, as well as Pediatric Emergency Medicine study personnel will identify potential research subjects. In addition, a full time research RN will be available to assist with identification and enrollment of potential subjects, if funding allows as mentioned above. Subjects that meet all inclusion and exclusion criteria and consent to participate will be enrolled.

b. Procedure for Recruitment of Participants

All patients who have physician-diagnosed asthma will be triaged upon arrival to the emergency department, and will be evaluated by a triage nurse. Upon identification of a patient with previously diagnosed asthma who is presenting with breathing difficulty or cough, the triage nurse will contact study personnel, either in the form of the research nurse (if available) or other study personnel who are available within the ED. Additionally, research personnel may identify subjects through periodic monitoring of the ED tracking board from the research office. Study personnel will approach the parent or guardian for potential study enrollment. As a part of screening for inclusion and exclusion criteria, study personnel will briefly explain the nature of the research project and perform baseline spirometry measurement prior to obtaining informed consent. Performance of this minimal risk study is considered by many to be standard of care in acute asthma, and will expedite screening of patients if performed prior to consent.

c. Procedure of Obtaining Informed Consent

Potential subjects and their parent or guardian will have the nature of the research study as well as potential risks and benefits of enrollment explained by study personnel. Consent will be obtained from the parent or guardian of all subjects, and assent obtained from subjects who are at least 7 years of age. A consent form written in English or Spanish will be provided to the parent/guardian based on their preferred language. A Spanish interpreter will be utilized as needed to answer questions and ensure clear understanding of expectations after enrollment. Subjects and parents will be given adequate time to consider enrollment, and questions will be encouraged and answered prior to enrollment.

d. Research Protocol

It will be explained to subjects and guardians that if enrolled in the study, that study participation will involve receiving an albuterol therapy with either the control or experimental nebulizer, assigned randomly, and performing follow-up spirometry testing after treatment. It will be explained that all of these therapies will occur within the DCMC ED, and will take approximately 20 minutes from start to finish. Subjects will be informed that if medically necessary, other treatments will be given, and that following participation, that standard of care treatment for their condition will be performed. A detailed description of the research protocol is provided in section VI above.

e. Timeline

This study is expected to begin enrollment in July 2015 and run through June 2017, though target dates may need to be adjusted based on ongoing analysis of enrollment rate, as well as the percentage of patients able to successfully provide spirometry data. Data cleaning and analysis will be completed by August 2017. The target abstract completion data is November

2017, followed by manuscript writing and submission. DCMC ED sees approximately 3000 visits for asthma annually. With research staff available at a minimum of 18 hours per day, we expect to have no issue achieving adequate enrollment for this study within a two-year period.

f. Privacy and Confidentiality of Participants

Study subjects will be assigned a unique identification number to protect their confidentiality through the course of the study period. A list linking subjects and identifiers will be maintained in a locked cabinet behind a locked door in the research office. Subject identity will remain strictly confidential and will only be accessible by the research team, unless disclosure is required by law.

g. Confidentiality of Research Data

Throughout the duration of the study, an electronic database will be maintained in a secure, password-protected, firewalled shared drive with access restricted to the research staff working directly on data analysis. Paper records including data collection forms containing patient identifiers, copies of a patient's medical chart, or other records containing protected health information (PHI), will be maintained in a study folder identified by study ID numbers. These folders will be kept in a locked cabinet located in a locked, badge-controlled facility. Once the database has been compiled and completed, PHI will be removed such that the only link between the study ID number and the patient will be a key, which will be stored separately from the study database. Data stored on the internal memory of the handheld spirometer will only be identified by the patient's study ID number without other PHI. All patient identifiers will be removed following data collection and analysis. All study records will be maintained at least as long as required by law. The data from this study may be published, but subject identities will not be disclosed.

h. Research Resources

Research personnel will consist of Pediatric Emergency Medicine (PEM) Fellowship faculty, PEM fellows, and the PEM Fellowship research nurse/coordinator. All of the research efforts of these people are reimbursed through the standard academic pay mechanism of the fellowship. No additional resources will be required. Equipment costs will be covered by the SERF grant. Any additional costs will be covered by the PEM Fellowship seed fund (if needed).

VIII. Potential Risks and Alternatives

There is a potential risk to patients of loss of confidentiality. This risk is minimized utilizing the methods described above. If the experimental nebulizer shows decreased efficacy compared to the control arm, subjects may experience less bronchodilation, and subsequently may require more subsequent doses of albuterol, or other adjunctive therapies. There is no reason to believe that patients in the experimental group will experience greater discomfort than those patients in the control group.

Data and safety Monitoring:
This study involves 2 FDA approved nebulizers that have been used clinically for decades.
The medication doses are similar to those used by children in the home setting. For these

reasons this study is considered very low risk and equivalent to the ED standard of care for non-study patients. Despite this, a Data and Safety Monitoring Plan will be in place for ongoing evaluation of the safety of this study. The DSMP will consist of the PI (Dr. Wilkinson) and the Co-I (Dr. Gardiner) reviewing any reported adverse events within 24 hours of occurrence. Additionally, at the midpoint of the study (subject #107), there will be a scheduled interim analysis. During this analysis we will analyze group difference with regards to adverse event and admission rates. If, during either of these reviews, new information is discovered that would change the risk profile of the study, enrollment will be suspended and the IRB will be notified to help determine a course of action.

IX. Potential Benefits

The potential benefit of this trial is the possibility of a better understanding of the effect of breath-enhanced nebulizer technology on the treatment of acute asthma. Additionally, if we are able to demonstrate significant benefit of this new technology, this may enhance the treatment of future pediatric patients with asthma, at home or in the emergency department. The potential benefit of this study to the individual study patient is largely unknown. Patients who are randomized to the experimental arm of the study may experience greater bronchodilation due to improved medication delivery; however, this benefit is likely minimal given that this study is evaluating only a single dose of albuterol.

X. Sites or Agencies involved in the research project

Research activities will be carried out exclusively at Dell Children's Medical Center.

XI. Review by another IRB

Not applicable.

XII. Citations

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