Positive Expiratory Pressure for the Treatment of Acute Asthma Exacerbations: A Randomized Controlled Trial

Nidhya Navanandan, MD[1], Monica Federico, MD[2], and Rakesh D. Mistry, MD, MS[1]

Objectives To evaluate the efficacy of brief, single administration of positive expiratory pressure (PEP) therapy in reducing clinical severity and need for additional second-line therapies and hospitalization in children presenting to the emergency department (ED) with acute asthma.

Study design This was a prospective randomized controlled trial of children 2-18 years of age presenting to a tertiary-care academic pediatric ED with moderate-to-severe asthma exacerbations from December 2014 to June 2016. Children who continued to have moderate asthma severity after completion of initial therapies (albuterol/ipratropium bromide and corticosteroids) were randomized to receive PEP therapy or standard of care. The primary outcome was change in pulmonary asthma score before and after intervention, as assessed by a blinded physician. Secondary outcomes included need for additional therapies, ED length of stay, and disposition.

Results A total of 52 patients were randomized to receive either PEP (n = 26) or standard therapy (n = 26). Study groups were similar in demographics and baseline characteristics. There was no significant difference in primary outcome between groups with a mean change in Pulmonary Asthma Score of 0.92 (±1.2) in the PEP group and 0.40 (±1.2) in the standard group ($P = .12$). There also was no significant difference in need for additional therapies, ED length of stay, and disposition. Mild, self-resolving side effects were observed in 3 subjects receiving PEP therapy.

Conclusion Single, brief, administration of PEP therapy after completion of first-line therapies does not improve clinical severity in children presenting to the ED with acute asthma. *(J Pediatr 2017;185:149-54).*

Trial Registration ClinicalTrials.gov: NCT02494076.

Asthma affects approximately 7 000 000 children in the US.[1] Acute asthma exacerbations are a leading cause of emergency department (ED) healthcare visitation. According to the National Center for Health Statistics, there are more than 750 000 ED visits and nearly 200 000 hospitalizations for children with acute asthma exacerbations each year.[2] As a result, childhood morbidity from asthma is substantial. Because children with acute asthma exacerbations frequently are treated in the emergency setting, ED visits represent an opportune time to implement interventions to reduce acute asthma symptoms and minimize the need for hospitalization.

Asthma exacerbations are characterized by airway obstruction and inflammation and airway hyper-responsiveness. Thus, treatments are aimed at reversing airflow obstruction, decreasing inflammation, and correcting the resultant hypoxemia.[3] The mainstay of ED therapy for children presenting with moderate and severe acute asthma exacerbations includes the administration of inhaled bronchodilators and corticosteroids. The National Heart, Lung, and Blood Institute guidelines recommend that initial therapies consist of 3 consecutive doses of inhaled selective β_2 agonists plus ipratropium bromide.[3] Concomitant administration of systemic corticosteroids at ED presentation also is recommended, because early administration is known to reduce symptoms and hospitalization rates.[4] Although these initial therapies consistently are administered in most EDs, clinical treatment and disposition after initial therapies are variable: some children have poor response and are hospitalized immediately, whereas others have excellent response and are observed and discharged home. A segment of children cannot be dispositioned immediately, and adjunctive second-line therapies are considered. There is no consensus, however, regarding the clinical decisions or choice of second-line treatments for children who fail to fully respond to first-line acute asthma therapy.

The approach to second-line asthma therapies is variable and may include use of agents such as continuous albuterol, subcutaneous epinephrine, intravenous terbutaline, and intravenous magnesium.[3] Recently, noninvasive positive pressure ventilation (NPPV) has been used as an experimental approach for treatment of children with respiratory failure due to severe asthma exacerbations.[3,5-9] NPPV is hypothesized

auto-PEEP	Auto-positive end-expiratory pressure
ED	Emergency department
PAS	Pulmonary Asthma Score
PEP	Positive expiratory pressure
NPPV	Noninvasive positive pressure ventilation
RT	Respiratory therapist

From the [1]Children's Hospital Colorado, University of Colorado School of Medicine, Section of Pediatric Emergency Medicine; and [2]Children's Hospital Colorado, University of Colorado School of Medicine, Section of Pediatric Pulmonary Medicine, Aurora, CO

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to improve respiratory status in acute asthma by stenting upstream airways and decreasing hyperinflation and auto-positive end-expiratory pressure (auto-PEEP) and by overcoming the added work of breathing due to auto-PEEP. There is concern, however, that positive pressure applied to these patients may contribute to air-trapping, ventilation-perfusion mismatch, and increased auto-PEEP.[10]

Typically, NPPV is used as a continuous therapy in the management of acute asthma; a novel approach is use of a single, brief administration of positive expiratory pressure (PEP). Similar to NPPV, PEP is thought to improve respiratory status in acute asthma by recruiting collapsed alveoli, reversing atelectasis, and improving ventilation-perfusion mismatch. In our institution, PEP has been used in a subset of children with asthma with refractory hypoxemia and/or respiratory distress after initial therapies, with anecdotal clinical improvement and reduced need for additional second-line therapies. Data on the efficacy of PEP in children with acute asthma, however, are lacking. Systematic investigations are necessary to determine the actual clinical effectiveness of PEP for acute asthma in the ED. The objective of this study was to evaluate the efficacy of brief, single administration of PEP for children with moderate-to-severe asthma exacerbations in the ED, specifically in improving clinical asthma severity and reducing need for additional second-line therapies.

Methods

This was a single-blinded randomized controlled trial that compared PEP with standard therapy in children presenting for moderate-to-severe asthma exacerbations who did not respond to first-line asthma treatments. Approval for the study was received from the Colorado Multiple Institutional Review Board. Written consent was obtained from all study participants. The study was registered at ClinicalTrials.gov (NCT02494076).

All children 2-18 years of age with a history of asthma presenting to an urban tertiary-care children's hospital ED for an acute asthma exacerbation were eligible for the study. To meet inclusion criteria, patients required (1) an established diagnosis of asthma, defined by at least 2 previous episodes of treatment with bronchodilators; (2) initial presentation to the ED with a moderate-to-severe asthma exacerbation, defined as a Pulmonary Asthma Score (PAS) ≥7; and (3) subsequent PAS ≥7 and <12 after completion of first-line therapies (3 doses albuterol/ipratropium bromide and corticosteroids). The PAS is a pediatric asthma severity scoring system adapted from previously validated scores and includes measures of respiratory rate, oxygen saturation, auscultory findings, retractions, and dyspnea (**Table I**; available at www.jpeds.com).[11-13]

Values from each category are summed, producing a total score between 5 and 15. Total scores <7 correspond with mild asthma exacerbations, whereas scores ≥7 and <12 indicate moderate asthma, and scores ≥12-15 indicate severe asthma. Children were excluded if they (1) did not complete first-line therapies; (2) immediately received a disposition (eg, admission or discharge) as determined by the treating clinician after completion of first-line therapies; (3) received prednisone or >2 albuterol nebulization treatments before presentation to the ED (eg, during emergency medical services transport or a primary care visit); (4) were deemed critically ill at presentation; or (5) were enrolled in the study previously. In addition, children with the following comorbid illnesses were excluded: facial or airway abnormalities, pneumonia, chronic lung disease, congenital heart disease, cystic fibrosis, or pneumothorax.

Study Protocol

After screening and consent by research assistants, eligible study subjects were assigned randomly into 1 of 2 study arms: "PEP" or "standard" therapy. Patients were randomized in blocks of 10. Children in both groups received standard first-line acute asthma therapy including combined nebulized ipratropium bromide 0.5 mg and albuterol (2.5 mg for less than 20 kg, 5 mg for 20 kg or more) for a total of 3 doses, and systemic steroids (prednisone 2 mg/kg to a maximum of 60 mg or dexamethasone 0.6 mg/kg to maximum of 16 mg). Immediately after completion of first-line medications, the treating respiratory therapist (RT) assessed for a qualifying PAS ≥7 and <12. If eligible, patients were approached for consent by trained research assistants and then randomized to either the PEP group or standard group. Subjects assigned to the PEP group received PEP therapy within 15 minutes of completion of first-line therapies, whereas subjects in the standard group received no additional therapies (**Figure 1**; available at www.jpeds.com). Blinded physicians assessed patients for PAS immediately after randomization and 15 minutes postcompletion of intervention or standard therapy. After the postintervention/control assessment, clinical care proceeded per the discretion of the treating physician. Both physician assessors and treating physicians were blinded to study assignments.

Per our hospital asthma clinical care guidelines, study subjects were monitored with oxygen saturation, respiratory rate, and heart rate measurements and received a PAS every hour until disposition. Subjects also were monitored for possible side effects from PEP therapy, including skin irritation, pneumothorax, and chest pain.

Subjects in the PEP group received brief, intermittent PEP therapy administered by the treating RT. PEP therapy was administered via EzPAP Positive Airway Pressure System (EzPAP, Smiths Medical, Dublin, Ohio), a compact device that provides PEP to prevent and reverse atelectasis. EzPAP can be used in all age groups as tolerated, with a mouthpiece or mask (**Figure 2**; available at www.jpeds.com). The device is driven by a gas source flow meter and is connected to an oxygen source. Air flow is monitored and adjusted to achieve desired expiratory airway pressures. Children <5 years of age received PEP via mask, and children ≥5 years of age used a mouthpiece for tolerability. Standardized measures for flow rate (start at 5 L/min), airway pressure (10-20 cmH_2O), and number (4 cycles) and duration of cycles (12 breaths per cycle) of PEP were used. Measures were determined by ED RTs by the use of established guidelines for PEP use at our institution. A wide range of goal airway pressure was chosen because of the variable airway compliance expected among study subjects.