The Journal of Emergency Medicine, Vol. 54, No. 1, pp. 40–46, 2018

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2017.08.099

Brief Report

A RANDOMIZED CONTROLLED TRIAL OF A SINGLE DOSE FUROSEMIDE TO IMPROVE RESPIRATORY DISTRESS IN MODERATE TO SEVERE BRONCHIOLITIS

Kristy Williamson, MD,* Gabriel Bredin, MD,† Jahn Avarello, MD,* and Sandeep Gangadharan, MD†

*Department of Pediatric Emergency Medicine, Cohen Children's Medical Center of New York, New Hyde Park, New York and †Department of Pediatric Critical Care Medicine, Cohen Children's Medical Center of New York, New Hyde Park, New York

Reprint Address: Kristy Williamson, MD, Department of Pediatric Emergency Medicine, Cohen Children's Medical Center of New York, 269-01 76th Avenue, New Hyde Park, NY 11040

☐ **Abstract—Background: Bronchiolitis is one of the most common disorders of the lower respiratory tract in infants. While historically diuretics have been used in severe bronchiolitis, no studies have looked directly at their early use in children in the emergency department. Objective: The primary objective of this study was to determine whether a single early dose of a diuretic in infants with moderate to severe bronchiolitis would improve respiratory distress. Secondary objectives examined whether it reduced the use of noninvasive ventilation and hospital length of stay. Methods: Patients diagnosed with clinical bronchiolitis were enrolled at a tertiary care, academic children's hospital over a 3-year period. This was a double-blind, randomized controlled trial in which subjects were randomly assigned to either furosemide or placebo. Respiratory rate and oxygen saturation at the time of medication delivery and at 2 and 4 h post-intervention were recorded, as well as other data. Exact logistic regression was used to examine associations. Results: There were 46 subjects enrolled and randomized. There was no difference in respiratory rates, measured as a decrease of ≥ 25%, at both 2 and 4 h after intervention between furosemide and placebo groups (odds ratios 1.13 and 1.13, respectively). There was also no difference in oxygen saturation, intensive care unit admission rate, or hospital length of stay between groups. Conclusions: While theoretically a single dose of a diuretic to reduce lung fluid would improve respiratory distress in children with bronchiolitis, our randomized controlled medication trial showed no difference in outcomes. ClinicalTrials.gov ID: NCT02469597.**

☐ **Keywords—bronchiolitis; diuretic; furosemide; pediatrics; infants**

INTRODUCTION

Bronchiolitis is one of the most common disorders of the lower respiratory tract in infants and young children. It is generally a self-limited disease, but accounts for much morbidity in the pediatric population, with > 100,000 admissions annually in the United Status and costs of up to $1.73 billion per year (1). Bronchiolitis is a clinical diagnosis, with symptoms including cough, fever, and difficulty breathing. Viral pathogens, such as respiratory syncytial virus (RSV) are the most common culprits for disease.

Few therapeutic interventions have proven beneficial in the treatment of bronchiolitis, and treatment varies widely among different physicians and institutions. Recent 2015 American Academy of Pediatrics (AAP) guidelines primarily recommend supportive care for infants with clinical bronchiolitis, generally advising against the routine use of albuterol, epinephrine, and systemic corticosteroids (2). Nonetheless, clinicians continue to seek various treatment strategies to improve the patients' respiratory distress.

Gabriel Bredin is currently at Department of Critical Care, Great Ormond Street Hospital for Children, London, United Kingdom.

Received: 23 January 2017; Final submission received: 7 August 2017;
Accepted: 11 August 2017

In bronchiolitis, there is oftentimes partial or complete occlusion of the distal airways due to local irritation with subsequent sloughing of mucosa and secondary airway edema with an increase in extravascular lung water. A notable study in adults with acute lung injury (ALI), a respiratory illness that also involves secondary airway inflammation, showed that fluid restrictive strategies were beneficial (3). Additionally, diuretics are commonly utilized as part of the chronic and acute management of children with chronic lung disease (4). In lieu of these data, physicians have proposed the use of fluid-restrictive strategies and diuretic use for children with pulmonary inflammation and extravascular lung water due to bronchiolitis. In bronchiolitis, there is damage and inflammation of the small bronchi and bronchioles. Edema and excessive mucous production due to viral infiltration of cells can lead to obstruction of airways (5). Furosemide is a sulfonamide-based loop diuretic that has been used in pediatric patients to reduce edema and mucous in both acute and chronic cardiovascular and pulmonary disease (6). However, to our knowledge, there are no studies looking at furosemide use to improve the lower airway obstruction commonly seen with bronchiolitis.

The aim of our study was to determine whether an early single dose of furosemide in moderate to severe bronchiolitis would improve respiratory distress. Specifically, we analyzed changes in respiratory rate, oxygen saturation, use of positive pressure ventilation (PPV) or intubation, and length of stay in children with bronchiolitis.

MATERIALS AND METHODS

This was a randomized, double-blinded, placebo-controlled study to assess the efficacy of a single dose of furosemide on hospitalized infants with clinical bronchiolitis. Patients were enrolled at a tertiary care, academic children's hospital from February 2013 to March 2016. In the emergency department (ED), infants with bronchiolitis were clinically recognized and treated based on the provider's judgment, as there was no current bronchiolitis clinical pathway followed at the time of study. Furthermore, there was no standard of care in terms of i.v. fluid administration for children with bronchiolitis or clinical dehydration. All children < 4 years of age diagnosed with clinical bronchiolitis and needing admission to the hospital as determined by the treating emergency physician were eligible for enrollment. Children < 4 years of age were originally included in our protocol in order to include a broader cohort, but ultimately only children < 2 years of age were included, based on recruitment by physicians. Exclusion criteria included the following: no legal guardian present, a sulfa medication allergy (due to a potential for cross-reactivity with furosemide), currently on diuretic therapy, presence of tracheostomy, hypotension or hemodynamic instability, use of supplementation oxygen at home, history of dialysis or renal disease, use of positive pressure ventilation at home, or enrollment in another drug intervention trial. Our Institutional Review Board approved all parts of the study, the study was registered with ClinicalTrials.gov, and all guardians signed informed consent before participation in the study. The study is reported in accordance with the Consolidated Standards for Reporting Trials (CONSORT) statement for randomized trials (7).

We aimed to recruit 98 patients for the trial. Based on clinical experience, we assumed that very few patients who would be admitted with bronchiolitis would have a significant response at 2 h post administration of placebo. To be conservative, it was assumed that the response to placebo would be no higher than 5%, and a clinically meaningful response rate would be significant improvement in 25% of patients at 2 h after administration of furosemide. The proposed sample size was 49 subjects per group to yield 80% power to detect such a difference using a χ^2 test with a 0.05 significance level.

Subjects were randomly assigned by a 1:1 ratio to either furosemide or placebo using a permuted block design. The randomization was also stratified by mode of delivery—i.v. or oral. A trained pharmacist then dispensed the appropriate intervention to be administered in a blinded manner by the patient's nurse or physician. The intervention was either a single dose of furosemide (1 mg/kg with a maximum of 10 mg) given orally or intravenously only if a peripheral i.v. line was already established, or a placebo of equal volume and consistency. The intervention was administered as early as possible in the patient's ED stay.

Only one single dose of furosemide was given in order to relate the medication to transient improvement in respiratory status, knowing that the medication has a half-life of approximately 6 h. Respiratory rate and oxygen saturation at the time of medication delivery, and at 2 and 4 h post-intervention, were recorded. We also logged demographic information and other variables, such as other treatments given before and after our intervention, use of noninvasive ventilation or intubation, and presence of a specific pathogen on respiratory viral panel testing.

A priori, we determined a clinically significant response would be a decrease of at least 25% in respiratory rate. We identified this outcome as opposed to a change in a clinical bronchiolitis score because the scores were not routinely documented by staff and because of the subjective nature of some components to the score. Age-appropriate respiratory rates were documented based on American Heart Association recommendations.