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Brief Report

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

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☐ **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.

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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.

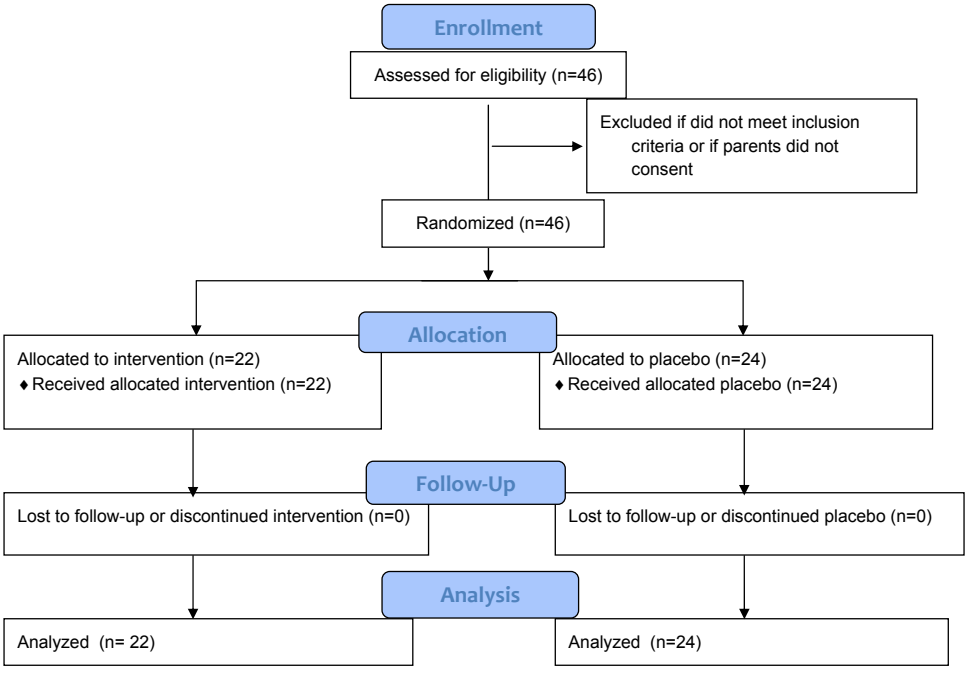

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) Flow Enrollment Diagram. Enrollment of patients in accordance with the CONSORT 2010 guideline for reporting of parallel group randomized controlled trials. The number of patients excluded from randomization was not documented, but all either did not meet inclusion criteria or parents did not consent. All patients were analyzed in their original groups.

Exact logistic regression was used to examine associations between the degree of response and treatment separately at 2 and 4 h. For each continuous outcome, such as percent changes in respiratory rate and oxygen saturation, analysis of covariance was used to examine the association between each outcome and treatment. Mode of delivery was included in each model as a covariate. Exact logistic regression was also used to examine the associations between intensive care unit (ICU) admission and PPV with treatment. Subgroup analyses were carried out to examine the effect of the presence of RSV virus on the association between treatment and each outcome. All but 2 patients were swabbed for a rapid viral panel, including testing for RSV.

RESULTS

Forty-six subjects agreed to participate and were randomized using CONSORT guidelines, 22 to the furosemide intervention and 24 to placebo (Figure 1). There were no significant differences between groups (Table 1).

There was no significant difference in respiratory rate, measured as a decrease of at least 25%, at both 2 and 4 h after intervention between furosemide and placebo groups

Table 1. Cohort Demographics Characteristics of Group Receiving Furosemide Intervention and Group Receiving Placebo

Characteristic	Entire Cohort (n = 46)	Furosemide (n = 22)	Placebo (n = 24)
Categorical factors, n (%)			
Sex			
Female	17 (37.0)	8 (36.4)	9 (37.5)
Male	29 (63.0)	14 (63.6)	15 (62.5)
Treatment with racemic epinephrine	40 (87.0)	20 (90.9)	20 (83.3)
Treatment with albuterol	30 (65.2)	15 (68.2)	15 (62.5)
PPV before intervention	4 (8.7)	1 (4.5)	3 (12.5)
Continuous factors, mean (SD)			
Age, mo	7.9 (6.2)	7.7 (5.5)	8.1 (6.8)
Weight, kg	7.9 (2.7)	7.6 (2.3)	8.0 (3.0)
Onset of symptoms, d	3.1 (1.8)	3.3 (2.1)	3.0 (1.5)
RR at time 0	45.4 (12.6)	48.0 (12.7)	43.1 (12.2)
SpO_2 at time 0	97.4 (2.8)	97.8 (2.6)	97.0 (2.9)

PPV = positive pressure ventilation; RR = respiratory rate; SD = standard deviation; SpO_2 = pulse oximetry.

Strata	Furosemide n=22 (%)	Placebo N=24 (%)	Difference between response rates Furosemide – Placebo (95% Exact Confidence Interval)
IV	1/11 (9.1)	2/11 (18.2)	-9.1 (-51.2, 35.6)
PO	3/11 (27.3)	2/13 (15.4)	11.9 (-27.5, 49.2)
Total	4 /22 (18.2)	4/24 (16.7)	1.5 (-26.4, 30.4)

Figure 2. Change in respiratory rate. Number of patients in the furosemide group and in the placebo group with a decrease in respiratory rate of ≥ 25% at 2 h post intervention. IV = intravenous; PO = per os (oral).

(odds ratio [OR] 1.13; 95% confidence interval [CI] 0.18–6.98; $p < 1.00$, Figure 2; OR 1.13; 95% CI 0.22–5.8; $p < 0.10$, respectively). For each continuous outcome, including percent change in respiratory rate and percent change in oxygen saturation at the two time points, there were no differences due to the intervention ($p < 0.80$ and $p < 0.77$, respectively, for respiratory rate, Figure 3; $p < 0.72$ and $p < 0.55$, respectively, for oxygen saturation).

Furthermore, there was no difference in ICU admission between furosemide and placebo groups (OR 0.56; 95% CI 0.11–2.49, $p < 0.58$) (Figure 4). There was no difference in length of stay (LOS) between groups, with LOS in the furosemide group of 2.8 days (standard error [SE] = 0.5) and LOS in the placebo group of 3.0 days (SE = 0.5) ($p < 0.90$). Finally, there was no difference in use of PPV between furosemide and placebo (OR 2.66; 95% CI 0.32–35.08; $p < 0.53$). No patients were intubated in the ED during the study.

The presence of RSV in these patients had no influence on respiratory rate, oxygen saturation, LOS, ICU admission, or use of PPV between groups.

DISCUSSION

While bronchiolitis remains very common, there has been no conclusive report of an intervention to reduce morbidity or hospitalization. Improvements in respiratory mechanics and clinical outcomes in ALI have been associated with conservative fluid management and the use of loop diuretics, such as furosemide, to reduce extravascular lung water (3,8–10). Our study evaluated whether a single-dose administration of furosemide would

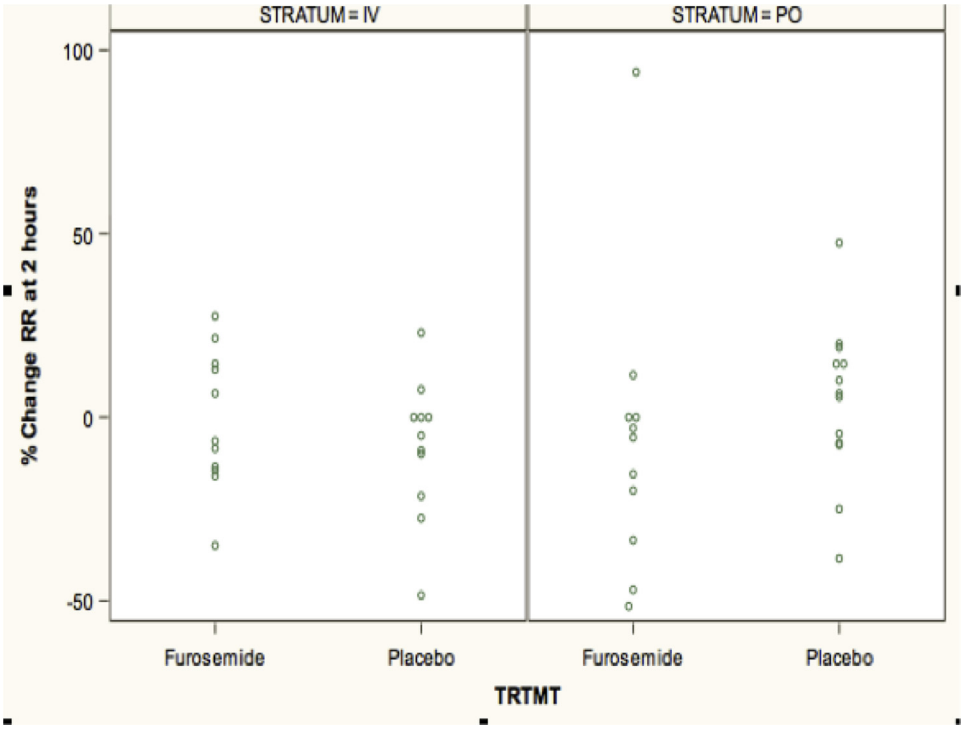

Figure 3. Change in respiratory rate (RR). Percent change in respiratory rate at 2 h after intervention (furosemide or placebo) in both intravenous (IV) and oral (PO) groups. TRTMT = treatment.

Strata	Furosemide n=22 (%)	Placebo n=24 (%)	Difference between response rates (95% Exact Confidence Interval)
IV	5/11 (45.5)	6/11 (54.5)	-9.1 (-51.2, 35.6)
PO	1/11 (9.1)	3/13 (23.1)	-14.0 (-50.0, 26.6)
Total	6/22 (27.3)	9/24 (37.5)	-10.2 (-38.4, 18.1)

Figure 4. Intensive care unit admissions. Number of patients admitted to the pediatric intensive care unit in the furosemide and placebo groups. IV = intravenous; PO = per os (oral).

improve clinical outcomes in children presenting to the ED with bronchiolitis.

We enrolled 46 patients who were randomized to receive either furosemide or placebo and then evaluated for a variety of clinically significant outcomes. There was no significant difference in physiologic variables between groups before or after the intervention. This suggests that a single dose of furosemide in the ED has no impact on tachypnea or hypoxia over the next several hours after administration. Additionally, the two groups of patients did not have any clinically significant differences for other important factors related to the morbidity of bronchiolitis, including hospital LOS, rate of admission to the ICU, or use of PPV.

Limitations

While our results do not suggest any clinically meaningful immediate benefit to furosemide administration in the setting of moderate to severe bronchiolitis, there are several important limitations to our study to consider. Our study did not meet our original enrollment goal, based on our sample size calculation to detect a 25% reduction in respiratory rate over the 3 years of study enrollment. The single greatest challenge we encountered to meeting enrollment goals was obtaining consent from parents to be included in the study. While it is clear that we did not observe any significant difference in any outcome between the two groups, it is possible that our results could be subject to a type II error, given that we did not meet our recruitment goal. It is also possible that a single-dose administration of furosemide may be insufficient to significantly impact extravascular lung water, and multiple doses may be necessary. Our study did not examine work of breathing, including use of accessory muscles or retractions, a variable that is oftentimes used in conjunction with other respiratory variables to determine severity of illness and need for admission. We did not include work of breathing, presence of fever, or a clinical bronchiolitis score due to the subjective nature of reporting. We also did not document amount of fluid (oral or i.v.) administered to the enrolled children or level of dehydration at presentation. Finally, our decision to include moderately ill infants with bronchiolitis in our inclusion criteria may have modified the impact of furosemide, and a focus on the severely ill bronchiolitis population could have demonstrated a more significant impact. Additionally, the AAP guidelines for the treatment of bronchiolitis were released during our study period, but we saw no major change in administration of nebulizer treatments in our cohort.

CONCLUSIONS

There is significant heterogeneity in the routine care of infants with bronchiolitis among clinicians (11–14). The use of furosemide in the management of bronchiolitis is not uncommon, though it is unproven. 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. This study, while limited by patient recruitment, adds further evidence to the current AAP recommendations to limit interventions to mainly supportive care in the routine care of children with bronchiolitis (15,16).

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ARTICLE SUMMARY

1. Why is this topic important?

This topic is important because bronchiolitis is such a common condition in infants and causes so much morbidity. Emergency physicians are constantly searching for any intervention aimed to improve the respiratory distress frequently seen, especially after the recent American Academy of Pediatrics (AAP) guidelines advising against the routine use of most medications.

2. What does this study attempt to show?

This study attempted to show how one early dose of a diuretic alters the respiratory status of infants with moderate to severe bronchiolitis.

3. What are the key findings?

There was no difference in respiratory rate, measured as a decrease of $\geq 25\%$ at both 2 and 4 h after intervention between furosemide and placebo groups. There was also no difference in oxygen saturation, intensive care unit admission rate, or hospital length of stay between groups.

4. How is patient care impacted?

This study adds further evidence to the current AAP recommendations for the management of bronchiolitis to limit interventions to mainly supportive care because an early dose of a diuretic does not change outcomes.