

A Randomized Trial of Nebulized 3% Hypertonic Saline With Epinephrine in the Treatment of Acute Bronchiolitis in the Emergency Department

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ACUTE BRONCHIOLITIS IS THE most common lower respiratory tract infection affecting children younger than 1 year.¹ Respiratory syncytial virus (RSV) is the most important pathogen responsible for acute bronchiolitis. The morbidity and mortality due to RSV infection is greatest in infants younger than

to 3% of high-risk infants annually, the optimal treatment for bronchiolitis remains unclear.² In addition, the rates of hospital admissions for bronchiolitis have increased substantially in North American infants during the last 2 decades.^{3,4} From 1980 to 2000, the rate of hospital admission for Canadian children with bronchiolitis increased from 15 to 39 admissions per 1000 children per year.³ In the United States, admission rates increased from 12.9 admissions per 1000 children in 1980 to 31.2 admission per 1000 children in 1996.⁴ Also, bronchiolitis admissions in the United States cost more than \$500 million annually, more than the cost of admission of any other respiratory disease, including cystic fibrosis (\$147 million per year).⁵

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3 months and in those with known risk factors such as prematurity, chronic lung disease, congenital heart disease, crowded living conditions, and tobacco smoke exposure.² Although it results in hospitalization of up to 1% of healthy infants and 2%

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With few effective treatments, the health care cost of managing bronchiolitis are significant; thus, any therapy that could decrease the severity of the illness and improve medical care could potentially offer substantial health care savings. In the past, several randomized controlled trials and a Cochrane review have suggested that bronchodilators may be effective therapy for patients with bronchiolitis.⁶⁻¹⁰ However, a meta-analysis published in 1997 determined that conclusive evidence for the efficacy of β_2 -agonist therapy for bronchiolitis remained unavailable.¹¹ In 2004, a systematic review of pharmacologic treatment of bronchiolitis in infants and children concluded that there was little evidence of the routine role of epinephrine, bronchodilators, corticosteroids, or ribavirin.¹² A Cochrane review and meta-analysis examining the efficacy of epinephrine in bronchiolitis concluded that there is some evidence that epinephrine may be favorable compared with salbutamol and placebo in outpatients.^{13,14}

Nebulized hypertonic saline has been shown to improve mucociliary clearance and sputum expectoration in patients with cystic fibrosis and with mucociliary dysfunction.¹⁵⁻¹⁷ It is hypothesized that hypertonic saline may be useful in bronchiolitis by absorbing water from the submucosa, thereby decreasing edema and improving mucociliary function. To date, there have been 4 trials investigating the use of nebulized 3% hypertonic saline solution in infants with viral bronchiolitis. In 2 of the studies, the improvement in the clinical severity scores was significant in the group treated with hypertonic saline.^{18,19} In the third and fourth studies, the hypertonic saline group had a clinically significant reduction in length of hospital stay.^{20,21} However, none of these studies were conducted in the emergency department (ED) setting, which is often the entry point to medical care for these children. A recent Cochrane Database Systemic Review of these 4 non-emergency-based trials (n=254) examined the role of hypertonic saline in acute bronchiolitis. The authors concluded that nebulized 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis.²²

To our knowledge, no study to date has examined the role of hypertonic saline in the ED for the treatment of bronchiolitis. Given the large number of patients who present to the ED with bronchiolitis as well as the uniqueness (time constraints, space issues, infection control, wait times) of the ED environment, we felt that this merited further investigation. We hypothesized that infants with bronchiolitis who were treated with hypertonic saline and epinephrine would have improved clinical severity scores, higher oxygen saturations, and lower admission rates than infants who were treated with our standard treatment, epinephrine and normal saline. We conducted a randomized, controlled superiority trial to answer this question.

METHODS

We conducted a randomized, double-blind controlled trial (with parallel design) in an urban tertiary care pediatric emergency department (Stollery Children's Hospital, Edmonton, Alberta, Canada). Ethics approval was granted by our local ethics board

and a clinical trial application for the study was approved by Health Canada. In addition, the trial was registered with Current Controlled Trials Ltd and assigned an ISRCTN number (66632312).

PATIENT SELECTION

Informed consent was obtained from the parent(s) of each child enrolled in the study. Infants were included if they had a chronological age of 6 weeks to 12 months, a clinical diagnosis of mild to moderate bronchiolitis (defined as the first episode of wheezing and clinical symptoms of a viral respiratory infection), an initial oxygen saturation of 85% or more but 96% or less on arrival to the ED, and if their initial Respiratory Distress Assessment Instrument (RDAI) score was 4 or higher.²³ Exclusion criteria were preexisting cardiac or pulmonary disease, previous diagnosis of asthma by a physician, any previous use of bronchodilators (except for treatment of the current illness), severe disease requiring resuscitation room care, inability to take medication using a nebulizer, inability to obtain informed consent secondary to a language barrier, or no phone access for follow-up. Hours of enrollment were typically from 4:00 PM to 2:00 AM and occasionally during the day if a research assistant was available. The trial was conducted from February 2004 to March 2005.

DESIGN

Physicians working in the ED performed a standard history and physical examination on all patients and assessed them for study eligibility. Research assistants collected data pertaining to demographics, medical history, current illness, and risk factors for asthma using a data collection form with standardized questions. The same research assistants, who were all trained by our ED clinical nurse educator, assessed outcomes. Patients were randomized into blocks of 4 (both throughout the bronchiolitis season and from month to month) to guarantee a comparable distribution of patients with different viral pathogens in each group. The randomization scheme was generated by the pharmacy using the Web site Randomization.com (<http://www.randomization.com>). Our pharmacy also prepared 2.5-mL aliquots of 0.9% normal saline and 2.5-mL aliquots of a second, indistinguishable solution of 3% hypertonic saline. The solutions were similar in appearance and smell, stored in identical syringes, labeled only by a code number, and placed in the research cupboard within the ED. The randomization list was concealed by the pharmacy until completion of the study. When the solution was given to the patient, the ED nurse added 0.5 mL of 2.25% racemic epinephrine to the randomization solution, and the total mixture of 3 mL was given to the patient by nebulization. Because the randomization process was determined by the pharmacy, emergency physicians, house staff, nurses, study personnel, and patients remained blinded to treatment allocation throughout the study.

Both groups received a dose of racemic epinephrine (diluted in either normal saline or hypertonic saline) at 0 minutes. Each treatment was given by nebulizer with continuous flow of oxygen at 6 L/min. All patients had measurements (respiratory rate, oxygen saturation, heart rate, and RDAI score) recorded at baseline (0 minutes) and repeated at 30, 60, 90, and 120 minutes. Each measurement was recorded after the patient's oxygen had been removed for a total of 5 minutes. A nasopharyngeal aspirate for virology (testing for RSV, influenza A and B, and parainfluenza) was obtained during the study, and the patient's baseline temperature was recorded. Two doses of the study drug were available for each patient such that, if the physician felt that a second dose of racemic epinephrine was

Table 1. Respiratory Distress Assessment Instrument^a

Variable	Points					Maximum Points
	0	1	2	3	4	
Wheezing						
Expiration	None	End	½	¾	All	4
Inspiration	None	Part	All	NA	NA	2
Location	None	Segmental, ≤2 of 4 lung fields	Diffuse, ≥3 of 4 lung fields	NA	NA	2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked	NA	3
Intercostal	None	Mild	Moderate	Marked	NA	3
Subcostal	None	Mild	Moderate	Marked	NA	3

Abbreviation: NA, not applicable.

^aWithin each variable, the subscores are summed to give a total score. The maximum point score for wheezing is 8; for retraction, 9.

needed during the 120-minute study period, the patient received the same drug combination again. Emergency department physicians were free to withdraw patients from the study or to use other interventions if deemed clinically necessary. Any adverse effects of the medications were recorded. Each family was contacted by telephone within 1 week to determine if any further treatment was sought after discharge from the ED.

OUTCOME MEASURES

The Respiratory Assessment Change Score (RACS) was the primary outcome variable. This is a clinical scoring system based on the RDAI and the change in respiratory rate. Although there is no criterion standard for assessing respiratory distress in bronchiolitis, the RDAI score is commonly used in other studies evaluating this illness.¹¹ This tool has demonstrated a high degree of interrater reliability, with a weighted κ of 0.94.²³ The RDAI score ranges from 0 to 17 points (**Table 1**).

The RACS is the sum of the change in the RDAI score plus a standardized score for the change in respiratory rate from 0 to 120 minutes. The change in respiratory rate is assigned 1 point per each 10% change in the respiratory rate. A decrease in the RDAI or in the respiratory rate during the study period is recorded as a positive change score. In the same way, a negative score signifies deterioration. The RACS calculates the sum of the change scores for each variable.²³

The second primary outcome for this study was the change in oxygen saturation from baseline to 120 minutes. The secondary outcome measures were rate of admission to hospital and rate of return to the ED.

STATISTICAL ANALYSIS

Sample Size Justification

Previous measurements of our primary outcome (RACS) in infants with bronchiolitis indicated that we could expect a standard deviation of approximately 3.^{23,24} We felt that anything less than a change of 3 points in the RACS would not be considered clinically significant. Assuming an α of .05 and a power of 90%, we required a total sample size of 46 infants to be able to detect a difference of 3 in the RACS between the 2 groups.

Data Analysis

The intention-to-treat principle was used in all of our analyses. Means and 95% confidence intervals are presented for all continuous outcomes. Rates are presented for dichotomous outcomes.

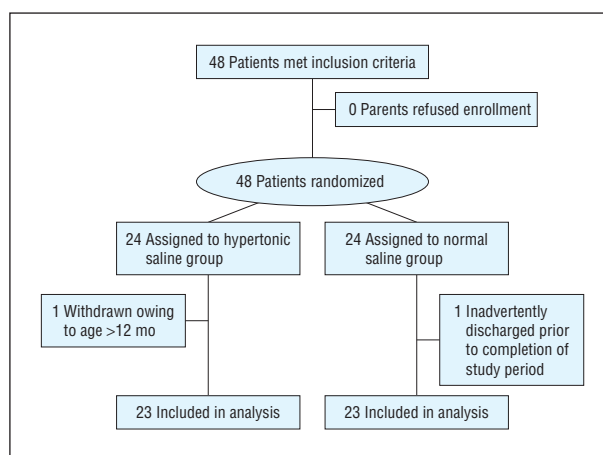


Figure. Enrollment and outcomes.

Continuous variables (ie, oxygen saturation, respiratory rate) were examined using the *t* test. Dichotomous data were examined using Fisher exact test. A linear multivariable regression analysis was performed to determine whether RACS was influenced by type of solution, administration of a second dose of the study drug, family history of asthma, sex, smoke exposure, age in days, and how well the infant fed. For the dichotomous variables (all except age), the parameter estimate can be interpreted as the average (adjusted) difference between the 2 groups. For age, the estimate is the average decrease in RACS score for every additional day of age.

All statistical analyses were done using SAS version 8.02 (SAS Institute Inc, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS

Forty-eight patients with viral bronchiolitis were enrolled in the study between February 2004 and March 2005 (**Figure**). Two patients (1 from each group) were excluded from analysis. One was withdrawn because he was older than 12 months, and the other was inadvertently discharged prior to completion of the study period. Overall, 45 of 46 patients (97.8%) had a nasopharyngeal swab for RSV to determine viral etiology. Patients were evenly divided between the 2 treatment groups (23 per group). The 2 groups had similar clinical char-

Table 2. Baseline Characteristics of the 2 Groups

Characteristic	Hypertonic Saline (n=23)	Normal Saline (n=23)
Male, No./total (%)	14/23 (60.9)	14/23 (60.9)
Mean (SD) age, mo	5.6 (4.0)	4.4 (3.4)
Family history of asthma, No./total (%)	15/23 (65.2)	17/23 (73.9)
Smoke exposure, No./total (%)	8/23 (34.8)	3/23 (13.0)
RSV positive, No./total (%)	19/23 (82.6)	18/22 (81.8)
Mean (SD) baseline RDAI score	9.2 (3.3)	8.7 (2.8)
Mean (SD) baseline O ₂ saturation	92.0 (3.0)	92.4 (2.5)
Mean (SD) baseline respiratory rate	54.8 (13.1)	53.5 (14.5)

Abbreviations: RDAI, Respiratory Distress Assessment Instrument; RSV, respiratory syncytial virus.

Table 3. Clinical Outcomes of the 2 Groups

Variable	Mean (95% CI)		
	Hypertonic Saline	Normal Saline	Difference
Change in RACS	4.39 (2.64 to 6.13)	5.13 (3.71 to 6.55)	0.74 (-1.45 to 2.93)
Change in O ₂ saturation	-0.44 (-2.11 to 1.23)	1.34 (-0.29 to 2.99)	1.78 (-0.50 to 4.06)

Abbreviations: CI, confidence interval; RACS, Respiratory Assessment Change Score.

acteristics and variables at baseline except for history of smoke exposure (**Table 2**). More infants in the hypertonic saline group were exposed to smoke than in the control group (34.8% vs 13.0%). However, a regression analysis showed that smoke exposure had no effect on the RACS.

CLINICAL OUTCOMES

Twenty-four patients received a second dose of the study drug (13 in the hypertonic saline group, 11 in the control group). The RACS from baseline (time 0) to 120 minutes demonstrated no difference in respiratory distress in the hypertonic saline group compared with the control group (normal saline). In addition, the change in oxygen saturation in the hypertonic saline group was not significant when compared with the control group (**Table 3**).

With respect to our secondary outcomes, the rate of return to the ED was not statistically significant when the 2 groups were compared. However, a lower proportion of patients in the hypertonic saline group were admitted to the hospital (8 of 23 vs 13 of 23 patients) than in the control group, reflecting an absolute difference in admission rate of 22%, although this difference was, again, not statistically significant (**Table 4**).

From the regression analysis, only 2 variables were found to have an effect on RACS: (1) a family history of asthma (with a positive family history, the RACS was more likely to be lower and therefore less significant) and (2) the age of the patient (the older the patient, the more likely the RACS was to be lower). Sex, type of solution, a sec-

Table 4. Secondary Outcomes

Variable	No./Total		RR (95% CI)
	Hypertonic Saline	Normal Saline	
Admissions to hospital	8/23	13/23	0.61 (0.22-1.19)
Returns to ED	3/23	4/23	0.74 (0.11-2.91)

Abbreviations: CI, confidence interval; ED, emergency department; RR, risk ratio.

Table 5. Regression Outcomes

Variable	Regression Coefficient	Parameter Estimate (95% CI)
Age, d		-0.0079 (-0.017 to 0.001)
Solution, normal saline: hypertonic saline	1:2	-0.63 (-2.83 to 1.57)
Second dose given, yes/no	1/2	0.37 (-2.12 to 2.86)
Family history of asthma, yes/no	1/2	-2.26 (-4.44 to -0.08)
Sex, male:female	1:2	-0.55 (-2.71 to 1.61)
Smoke exposure, yes/no	1/2	-1.03 (-3.83 to 1.77)
Infant feeding well, yes/no	1/2	-0.92 (-3.27 to 1.43)

Abbreviation: CI, confidence interval.

ond dose of the test solution, feeding, and smoke exposure did not influence RACS (**Table 5**).

Adverse effects were noted in 4 infants (vomiting, 3; diarrhea, 1); all were enrolled in the hypertonic saline group. No additional bronchodilators were given to any enrolled patient during the study period.

COMMENT

To our knowledge, this is the first study examining the role of hypertonic saline in the treatment of bronchiolitis in the ED setting. Our study showed that 1 to 2 nebulizations of hypertonic saline mixed with racemic epinephrine is no more effective than the same number of nebulizations of normal saline mixed with racemic epinephrine in the treatment of bronchiolitis in the ED, as determined by a clinical scoring system (RACS). Although both intervention groups demonstrated clinically meaningful improvements in respiratory distress, we observed no differential benefit for our experimental group (hypertonic saline and racemic epinephrine) compared with our current standard of care (normal saline and racemic epinephrine).

To have clinical relevance, we decided a priori that a change in the RACS of at least 3 points would be important. In both treatment groups, the mean RACS was greater than 3 (5.13 in the control group and 4.39 in the hypertonic saline group), suggesting that either drug combination improves clinical scores in bronchiolitis.

We feel that our study was adequately powered for RACS as our primary outcome, based on an α of .05 and a power of 90%. The total sample size required was 46 infants, and this was achieved. Our patient population in the study showed male predominance (60.9%), an av-

erage age of 5.0 months, and a primary rate of infection with RSV of 82.2%. These patient characteristics are similar to those in previous studies. Despite these similarities, hypertonic saline does not appear to have an effect on the acute ED presentation of bronchiolitis in the 1 to 2 doses given in our study. Effectiveness has already been shown in the ambulatory and in-patient settings, with an increased number of doses of hypertonic saline in those studies.¹⁸⁻²¹ Interestingly, however, in our trial the hospital admission rate was lower, though not statistically significant, in the hypertonic saline group. The admission rate was 22% lower in this group, a difference that may have been significant if the number of infants enrolled in the study was larger. This outcome measure seems to be quite relevant, given the potential effect on resource allocation and staffing.

There are 4 previously published studies on the use of hypertonic saline in bronchiolitis. The earliest was published in 2002 and included 65 infants with bronchiolitis in the ambulatory setting who were randomized to receive either terbutaline and normal saline or terbutaline and 3% hypertonic saline 3 times a day for 5 days. The authors noted a significant improvement in the clinical score after treatment with hypertonic saline on each of the 5 days in this modestly sized study.¹⁸ The authors commented that the same effect might not have been seen if the infants had had a more severe clinical score. Their study infants had mild bronchiolitis, and only 7% were hospitalized,¹⁸ compared with our hospitalization rate of 45%. The other studies were conducted in hospitalized patients. In the most recently published study (2007) of treatment of bronchiolitis with hypertonic saline, hospitalized patients were randomized to receive repeated doses of either hypertonic saline or normal saline in addition to routine therapy ordered by the attending physicians. However, bronchodilators were prescribed approximately 5 times a day in addition to the study solution, making it difficult to state how much of an added effect the bronchodilators had. Overall, the authors found a clinically relevant reduction in length of hospital stay in the hypertonic saline group.²¹ In the third study, 52 hospitalized patients with bronchiolitis were enrolled in an initial trial. Patients were randomized to either epinephrine in normal saline or epinephrine in 3% hypertonic saline. Treatments were given 3 times a day until discharge. A further 41 infants were enrolled for a second year, and the pooled data published 3 years later showed significant improvement in the clinical severity scores in the group treated with hypertonic saline as well as a shortened hospital stay in the same group.^{19,20} While each of these 4 studies showed a positive effect in improving clinical severity scores after treatment with hypertonic saline, no study examined infants in the emergency setting, which is often the first point of contact with medical care, and may represent a heightened degree of acuity.¹⁸⁻²¹ The ED is also different from the inpatient or ambulatory setting in that patients are undifferentiated on initial presentation, treatment options and resources may be limited, and the opportunity to watch the disease process evolve over time might not exist.

Adverse effects encountered with the use of hypertonic saline are rare and infrequent. Wark and McDonald¹⁷

described an excellent safety profile for hypertonic saline after studying 143 patients with severe cystic fibrosis who were treated with hypertonic saline solution inhalations. There is a reported risk of bronchospasm and of decreased ciliary beat frequency; however, these are usually only seen with higher concentrations of hypertonic saline (>7%).²⁵ In our study, we used a 3% hypertonic saline solution to decrease the risk of the above adverse effects. In addition, by giving the hypertonic saline with epinephrine, a bronchodilator, any additional bronchoconstriction effect secondary to the hypertonic saline was avoided. All previous studies have also used 3% hypertonic saline; however, future studies could clarify the role of higher hypertonic solutions in treating bronchiolitis.

Although we did not have 24-hour recruitment coverage for the duration of this study, all of the eligible families approached for participation were successfully enrolled. The current standard of care for bronchiolitis differs from one hospital to another in North America, raising the question of the generalizability of these findings. However, there seems to be some reasonable evidence for the use of both epinephrine and hypertonic saline in this illness, making this study clinically relevant.

We did not include a traditional (no drug intervention) placebo group in this investigation, as this would conflict with the current practice in our institution; thus, we are uncertain of the effect of racemic epinephrine alone in the treatment of bronchiolitis. It appears that racemic epinephrine has an independent and positive effect on bronchiolitis in the outpatient setting,¹³ and the added benefit of hypertonic saline is unclear, given the acuity of the patient population.

As our research team provided a maximum of 2 doses of the study drug, we may have been unable to deliver a comparably intensive dose in relation to previous research. All previous studies with hypertonic saline gave multiple doses of hypertonic saline over an extended period of time, and perhaps our results would have been different had we used more than 1 to 2 doses of hypertonic saline or measured the respiratory parameters for longer than 120 minutes.¹⁸⁻²¹ In addition, the duration of hypertonic saline effect (half life) is presently unknown.

The optimal treatment of bronchiolitis remains unclear. Our study showed no clinically significant improvement in clinical severity with hypertonic saline in the emergency setting compared with normal saline when a maximum of 2 doses were used. However, there seemed to be a trend toward decreased rates of hospitalization in the hypertonic saline group. The ED setting differs from that of the ambulatory or inpatient setting in that interventions are constrained by time, space, and resources. The significance of this study is that this venue (the ED) is often the initial point of contact for many infants with bronchiolitis. As this is the first study with hypertonic saline in the emergency setting and the first negative study, the need for further research is clearly evident to determine whether hypertonic saline does, in fact, have a role in the treatment of bronchiolitis in the ED setting.

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