A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis

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Objective: In previously well infants hospitalized with acute viral bronchiolitis, the effectiveness of repeated nebulized therapy with epinephrine (EPI) was compared with treatment with albuterol (ALB) or saline placebo (PLAC).

Study design: In this randomized, double-blind, parallel-group, controlled trial, infants received study nebulizations every 1 to 6 hours and were assessed twice daily by the research team. The primary outcome was length of hospital stay (LOS). Secondary outcomes included the time from admission until the infant had normal hydration, oxygenation, and minimal respiratory distress.

Results: A total of 149 infants were randomized; 50 were allocated to receive racemic EPI, 51 were given ALB, and 48 received PLAC. Baseline characteristics and pre-enrollment symptoms, signs, and therapy were similar between groups. There were no group differences in the primary outcome measure, mean LOS (hours) (± SD): EPI = 59.8 (62), ALB = 61.4 (54), and PLAC = 63.3 (47); P = .95 by intent-to-treat analysis. Group differences were not statistically significant in any of the secondary outcomes.

Conclusions: There were no group differences in the effectiveness of therapy for infants hospitalized with bronchiolitis. Based on these results, we do not recommend routine use of either nebulized EPI or ALB in this patient group. (J Pediatr 2002;141:818-24)

Only supportive therapy is available for acute viral bronchiolitis, most of whom have been previously well.1 β-2 agonists, such as albuterol (ALB), remain the mainstay of treatment,2,3 but their efficacy has been questioned in two meta-analyses.4,5

Epinephrine (EPI), an α-adrenergic agent, has potent vasoconstrictive properties and may reduce airway edema and mucous production,6-12 hallmarks in the pathologic features of bronchiolitis. Short-term (<3 hours) benefits in oxygenation, respiratory rate, and clinical severity score have been observed,6-11,13 but the potential benefits of extended use required study. On the basis of the positive short-term results, we hypothesized that extended-use epinephrine would provide a measurable decrease in the respiratory distress of infants hospitalized with moderate-to-severe bronchiolitis. The length of hospital stay (LOS) was chosen as the primary outcome measure because it was a comprehensive measure of the infant’s well-being, which incorporated the time required for resolution of respiratory distress, hypoxemia, and poor feeding. Thus, our goal was to compare the effectiveness of repeated nebulized EPI compared with ALB and saline

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placebo (PLAC) in this group of infants.

**Methods**

**Study Design**

This study was a double-blind, randomized placebo-controlled, parallel-group trial, approved by the Scientific Review Committee of the Montreal Children’s Hospital (MCH) Research Institute and by the MCH Institutional Review Board.

**Study Setting**

Infants were recruited throughout two successive bronchiolitis winters (mid November to March; 1998-1999 and 1999-2000) at the time of hospital admission from the emergency department (ED).

**Study Participants**

Eligible infants included all previously well infants (aged ≤12 months) with a clinical diagnosis of acute viral bronchiolitis who were hospitalized during the study period because of: (1) hemoglobin oxygen saturation of <95% in room air, (2) poor feeding with or without dehydration, (3) lethargy, (4) sustained tachypnea with a resting respiratory rate of ≥70 breaths/minute, or (5) the global impression of need for admission by the attending ED physician. Bronchiolitis was clinically defined as the first episode of wheezing in an infant and evidence of an acute respiratory tract infection (coryza or body temperature >38°C rectal or cough). Infants were excluded from participation if they were older than 12 months; had a previous history of wheezing or home bronchodilator use; or if they were directly transferred to the intensive care unit. Infants were also excluded if they had: (1) a gestational age at birth of <34 weeks, (2) underlying chronic cardiac or pulmonary disease (eg, bronchopulmonary dysplasia), (3) immunocompromise, or (4) history of immunoprophylaxis therapy (ie, respiratory syncytial virus (RSV) immune globulin or RSV monoclonal antibody therapy). Infants with a parent not fluent in either English or French were also excluded.

**Randomization, Allocation, and Treatment Groups**

Computer-generated randomization within blocks with 6 subjects was used to assign patients to one of three treatment strategies: racemic EPI (0.03 mL/kg/dose of a 2.25% solution); ALB (0.03 mL/kg/dose of a 5 mg/mL solution) (Ventolin, GlaxoSmithKline, Mississauga, Ont, Canada); or PLAC (0.03 mL/kg/dose of 0.9% sodium chloride). Treatment was allocated in the emergency department (ED) by the Department of Pharmacy, with the code for medication allocation held by our study pharmacist who had no contact with the study participants.

**Blinding**

All study solutions were identically clear, colorless, and odorless. Equal volumes of medication, dispensed in opaque bottles, were prepared in advance with standard dosing units and were numerically coded for the use of attending physicians, ward nurses, and the study nurses. All study personnel and participants were blinded to treatment assignment for the duration of the study. To evaluate blinding, parents, ward staff, and the research nurse for each enrolled patient were questioned about which therapy they believed the infant received.

**Procedures**

Nebulizations were administered for 10 to 15 minutes with a small, tight-fitting plastic face mask with an updraft nebulizer with continuous flow of 100% oxygen at 6 to 7 L/min. Infants received nebulizations every 1 to 6 hours, with frequency changes made at the discretion of the attending medical care team. All infants with a hemoglobin oxygen saturation in room air of ≥95% received continuous supplemental humidified oxygen. Oral or intravenous fluid supplementation was provided by using standard guidelines for the management of dehydration in infants. All randomized infants were assessed twice daily for the duration of their hospital stay with documentation of the infant’s vital signs, hemoglobin oxygen saturation during quiet rest, oxygen needs, hydration status, and nebulization requirements. Respiratory distress was measured by using the Respiratory Distress Assessment Instrument (RDAI), a 17-point categorical score, developed by Lowell et al. This score, which measures wheezing and chest wall retractions, was chosen because of its face validity, high inter- and intrarater reliability and its discriminative ability.

**Measurements/Outcomes**

The primary study outcome, LOS, was defined as the time between study entry and the actual time that the infant left the in-patient ward, as noted by the ward staff. Study entry was defined as the time that the consent form was signed; this occurred in the ED after the decision to admit was made by the attending ED physician. A priori, a 24-hour group difference in LOS was considered a clinically meaningful indication of benefit, from both parental and health care system perspectives.

Secondary outcomes of interest were: time from admission until the infant had normal oxygenation (a hemoglobin oxygen saturation of ≥95% in room air); adequate fluid intake to meet maintenance requirements (50 mL/kg/12 hours); and minimal respiratory distress, indicated by an RDAI score of ≤417 and minimal requirement of nebulized medications (frequency of treatments less often than every 4 hours). In breast-fed infants, we used a consensus agreement from the mother and attending nurse to determine when fluid intake was satisfactory. Criteria for discharge from the hospital included: no need for supplemental fluids or oxygen; nebulizations not required more often than every 4 hours; and minimal re-
spiratory distress. We systematically searched for tachycardia, tremor, and hypertension. Follow-up outcomes, assessed by standardized telephone interview 7 days after hospital discharge included the rates of ED return visits; re-admission to the hospital; admission to the intensive care unit; and return visits to a primary care giver.

Sample Size and Statistical Methods

To detect a mean decrease of 24 hours in LOS between the three treatment groups, with an α of .05 and power of 80%, we required 177 patients (59 per group). This was based on the prestudy mean LOS at MCH of 120 ± 48 hours. A blinded interim analysis to assess safety outcomes and check the quality of the randomization was planned and performed between bronchiolitis seasons, after approximately half of the patients were recruited into the study. α levels were adjusted according to O’Brien-Fleming stopping rules and the decision was made to continue the trial. An independent data monitoring committee reviewed the blinded results of 149 infants after the second bronchiolitis season and recommended no further patient recruitment.

The primary analysis was performed according to intention-to-treat guidelines for enrolled patients, regardless of withdrawals or protocol deviations. Mean group difference in continuous variables, including the primary outcome, LOS, were analyzed using 1-way analysis of variance techniques. In the secondary analyses, Kaplan-Meier survival curves were constructed to explore the group differences in the time to hospital discharge; normal oxygen saturation; adequate fluid intake; and minimal respiratory distress. Cox proportional hazards regression was used to evaluate potential confounders. Group differences in the baseline characteristics were evaluated descriptively and clinically relevant group differences were examined for potential confounding. The twice-daily measurements (including

Fig 2. Survival curve results by treatment group, over time in hours. I, Proportion of patients remaining in hospital (LOS); II, Proportion of patients without normal oxygenation (hemoglobin oxygen saturation ≥95% in room air); III, Proportion of patients with unsatisfactory oral intake.
respiratory rate, RDAI score, and hemoglobin oxygen saturation) were evaluated with repeated-measures analysis of variance. Interobserver reliability for the RDAI was tested by using the weighted \( \kappa \) coefficient; a \( \kappa \) value of \( \geq 0.8 \) was considered satisfactory.

**RESULTS**

During the study, 495 infants with bronchiolitis were hospitalized and 149 infants entered the study. Reasons for exclusions are detailed in Fig 1 along with patient allocation by treatment group. Fifty infants were allocated to racemic EPI, 51 were given ALB, and 48 received PLAC. The overall mean age of infants was 4.3 months; 71% had RSV-positive nasopharyngeal aspirates. All infants had audible wheezing and cough. Coryza was present in 116 (78%) and fever in 78 (52%). Upon admission, poor feeding was reported in 129 (87%) and lethargy in 94 (63%). There were no significant group differences (Table I) in baseline characteristics including ethnicity, mean age, gestational age, mode of feeding, passive cigarette exposure, atopic features, and mean duration of symptoms before study enrollment. There were slightly more male subjects in the ALB group (69% vs 56% [EPI] and 52% [PLAC]).

<table>
<thead>
<tr>
<th>Comparison</th>
<th>EPI (n = 50)</th>
<th>ALB (n = 51)</th>
<th>PLAC (n = 48)</th>
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<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
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<tr>
<td>Males, n (%)</td>
<td>28 (56)</td>
<td>35 (69)</td>
<td>25 (52)</td>
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<tr>
<td>White, n (%)</td>
<td>35 (70)</td>
<td>37 (73)</td>
<td>35 (73)</td>
</tr>
<tr>
<td>Mean age (mo)(SD)</td>
<td>4.2 (5.1)</td>
<td>3.9 (2.9)</td>
<td>4.7 (2.9)</td>
</tr>
<tr>
<td>Gestational age (wk)(SD)</td>
<td>38.5 (1.8)</td>
<td>38.9 (1.8)</td>
<td>38.9 (1.7)</td>
</tr>
<tr>
<td>Breast-fed, n (%)</td>
<td>21 (42)</td>
<td>24 (47)</td>
<td>28 (58)</td>
</tr>
<tr>
<td>Mother smokes cigarettes, n (%)</td>
<td>12 (24)</td>
<td>13 (25)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Eczema, n (%)</td>
<td>10 (20)</td>
<td>9 (18)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Family history of asthma in 1st degree relatives, n (%)</td>
<td>16 (32)</td>
<td>17 (33)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Mean duration of illness pre-enrollment (ds)(SD)</td>
<td>5.5 (5.7)</td>
<td>4.9 (2.6)</td>
<td>4.5 (3.1)</td>
</tr>
<tr>
<td><strong>Pre-enrollment ED therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received oxygen, n (%)</td>
<td>13 (26)</td>
<td>12 (24)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Antibiotic therapy, n (%)</td>
<td>9 (18)</td>
<td>14 (27)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Received nebulized ALB (%)</td>
<td>35 (70)</td>
<td>40 (78)</td>
<td>40 (85)</td>
</tr>
<tr>
<td>Mean number of ALB nebulizations (SD)</td>
<td>2.9 (2.0)</td>
<td>2.6 (1.8)</td>
<td>2.6 (1.5)</td>
</tr>
<tr>
<td>Received nebulized EPI, n (%)</td>
<td>18 (36)</td>
<td>21 (41)</td>
<td>18 (38)</td>
</tr>
<tr>
<td>Mean number EPI nebulizations (SD)</td>
<td>1.5 (0.7)</td>
<td>1.5 (0.9)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td><strong>Baseline physical features</strong></td>
<td></td>
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<tr>
<td>Number RSV-positive, n (%)</td>
<td>35 (78)</td>
<td>40 (87)</td>
<td>31 (74)</td>
</tr>
<tr>
<td>Mean respiratory rate (breaths/minute) (SD)</td>
<td>52 (15)</td>
<td>56 (14)</td>
<td>56 (15)</td>
</tr>
<tr>
<td>Mean heart rate (beats/min) (SD)</td>
<td>160 (20)</td>
<td>156 (19)</td>
<td>154 (19)</td>
</tr>
<tr>
<td>Mean % oxygen saturation in room air (SD)</td>
<td>96 (5)</td>
<td>95 (3)</td>
<td>96 (4)</td>
</tr>
<tr>
<td>Median RDAI score (range)</td>
<td>7 (1-12)</td>
<td>6.5 (0-16)</td>
<td>7 (0-14)</td>
</tr>
<tr>
<td>Pneumonia on chest radiograph (%)</td>
<td>14 (38)</td>
<td>16 (42)</td>
<td>12 (29)</td>
</tr>
</tbody>
</table>

The mean number (± SD) of study nebulizations received was similar in each treatment group: EPI = 12 (SD = 10), ALB = 12 (SD = 10), and PLAC = 16 (SD = 15) \((P = .13)\). There were no significant group differences in co-interventions including: concomitant antibiotic therapy, chest physiotherapy, and nasal suctioning. There were 10 withdrawals during the study (EPI = 1, ALB = 4, PLAC = 5); all were RSV-positive (Fig 1, available at The Journal of Pediatrics Online at www.mosby.com/jpeds).

There were no significant group differences in the primary outcome, mean LOS (hours)(± SD): EPI = 59.8 (62), ALB = 61.4 (54), and PLAC = 63.3 (47); \( P = .95 \), by intent-to-treat analysis, nor in the secondary analysis using survival curve methods \((P = .89)\) (Fig 2, I).
Table II. Results: Primary and secondary outcomes of interest

<table>
<thead>
<tr>
<th>Outcomes (h)(SD)</th>
<th>EPI</th>
<th>ALB</th>
<th>PLAC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LOS</td>
<td>59.8 (62)</td>
<td>61.4 (54)</td>
<td>63.3 (47)</td>
<td>.95</td>
</tr>
<tr>
<td>Mean time to normal oxygenation (hemoglobin oxygen saturation of ≥95% in room air)</td>
<td>25.0 (37)</td>
<td>33.0 (55)</td>
<td>36.6 (56)</td>
<td>.5</td>
</tr>
<tr>
<td>Mean time to adequate fluid intake</td>
<td>35.1 (44)</td>
<td>38.4 (42)</td>
<td>47.6 (48)</td>
<td>.4</td>
</tr>
<tr>
<td>Mean time to RDAI ≤4</td>
<td>34.6 (54)</td>
<td>45.7 (55)</td>
<td>56.8 (44)</td>
<td>.4</td>
</tr>
<tr>
<td>Mean time to infrequent nebulizations (every 4 h or less often)</td>
<td>16.5 (30)</td>
<td>31.1 (48)</td>
<td>34.3 (46)</td>
<td>.08</td>
</tr>
</tbody>
</table>

There was no significant change in mean LOS (hours)(± SD) when patients withdrawn from the study were excluded from analysis: EPI = 60.3 (63), ALB = 53.5 (41), and PLAC = 54.7 (36); P = .77. In consideration for the asymmetric distribution for LOS, secondary analyses were also conducted using log transformation of the means (EPI = 5.75 (0.78), ALB = 5.80 (0.80), and PLAC = 5.86 (0.82); P = .79) and nonparametric comparison of medians (Kruskal-Wallis test) (EPI = 56.0, ALB = 43.9, and PLAC = 51.2; P = 0.55); there were no significant group differences. There were no statistically significant group differences in any of the secondary outcomes of interest: mean time to normal oxygenation (hemoglobin oxygen saturation of ≥95% in room air) (Fig 2, I), mean time to adequate oral intake (Fig 2, III), mean time to RDAI ≤4, and mean time to infrequent nebulizations (every 4 hours or less often) (Table II). In the repeated measures analyses, all groups had a similar rise in hemoglobin oxygenation and decrease in respiratory rate and RDAI score.

Follow-up outcomes were similar between groups. Overall, 95 (62%) (EPI overall, 95 (62%) (EPI = 32, ALB = 28, PLAC = 35) infants had a medical visit in the week post discharge. Of these, the reason for the visit was: check-up (N = 67), baby not better (N = 5), baby worse (N = 6), and for an unrelated reason (N = 15). Eight of the medical visits were to the ED (EPI = 1, ALB = 3, and PLAC = 4); 3 infants (PLAC) were re-admitted. Adverse effects included asymptomatic transient (<1 hour) tachycardia, mild hypertension, and slight tremor; these were similar between treatment groups. One infant (ALB) was transferred to the intensive care unit for 48 hours but did not require intubation or mechanical ventilation.

Double-blinding was maintained throughout the study; when asked to guess the allocation group, the majority of respondents (research nurses = 70%, ward nurses = 77%, parents = 74%) replied that they “did not know” which therapy the infant received. Of those who did choose to guess allocation, few guessed correctly (research nurses = 17%, ward nurses = 4%, parents = 11%). There was no difference in the proportion of correct guesses by treatment group.

**DISCUSSION**

We found no clinically significant difference in the primary outcome measure, LOS, in infants treated with extended-use nebulized EPI compared with those who received either nebulized ALB or PLAC. This observation was supported by the lack of significant group differences in all secondary and follow-up outcomes including the time to normal oxygenation; adequate fluid intake; RDAI clinical score ≤4; infrequent nebulizations; and revisit and re-admission rates. Results from the primary intent-to-treat analysis, and those from secondary analyses excluding withdrawn patients, yielded similar results.

In this study we were careful to avoid the pitfalls of previous trials that were highlighted in the two recent meta-analyses on bronchodilator use in infants with bronchiolitis4,5 such as patient heterogeneity, lack of description of potential confounders, and outcome measures of questionable clinical importance. In this trial, only previously well infants with first-time wheezing were included, thus reducing the risk of including young children with true asthma. We documented potential confounders such as prestudy duration of illness, baseline severity, and atopic history. Admission and discharge criteria were explicit. Blinding was maintained throughout the study period. Rather than determining short-term differences, like a change in respiratory rate pre- and post-study nebulization, we selected relevant outcomes that reflected the condition of the infant over the entire duration of hospital stay; both globally (LOS) and more specifically with the secondary outcome measures.

We believe that the lack of benefit from either EPI or ALB is related to the unique pathologic features of viral bronchiolitis and the anatomic features of the young infant. The extent of bronchiolar epithelial necrosis and the speed of ciliated epithelial regeneration are likely limiting factors that influence recovery from the illness. In turn, these features probably depend on viral type, viral load, and individual host variables.
Although EPI may be useful in edema reduction, by the time infants present to medical care, the amount of necrosis may already be substantial. Although definitive proof is lacking, other researchers have suggested that infants may have inadequate β-agonist lung receptor sites or immature bronchial smooth muscle development to account for the lack of pulmonary improvement after treatment with bronchodilator agents, such as albuterol.19-22

The short-term benefits in respiratory rate, oxygen saturation, and clinical score that have been observed with epinephrine6-11,13 and the subtle improvements in clinical score that have been previously reported with albuterol15,16,23 may, in fact, be more a reflection of the general stimulant properties of these two medications, as opposed to a therapeutic pulmonary effect.

We recognize that the use of saline in the placebo arm of this trial was controversial. Some have suggested that even small quantities of saline act as a pulmonary irritant and may induce hypoxia and bronchoconstriction. Nonetheless, if detrimental, the benefits of the two treatment arms would have been falsely magnified.

After recruitment of 149 infants, the blinded independent data monitoring committee found that there was 80% power to show a 30-hour difference in LOS between groups and 75% power to show the intended 24-hour difference in LOS, with an α level of .05. A blinded sensitivity analysis was conducted, using as many as 20 additional hypothetical patients in each treatment group for a total sample of 209 infants. The LOS in hypothetical patients ranged between 60 and 80 hours, compared with the overall true mean LOS of 61.5 hours. The results reached neither statistical significance nor a difference between groups of 24 hours. Based on the lack of difference between the treatment arms and this sensitivity analysis, the panel recommended against recruiting any additional patients. We did not aim to examine group differences of <24 hours; this would involve multicenter study of an exponentially greater number of infants. Small differences may exist but the clinical relevance of these in unclear.

We conclude that extended-use nebulized EPI did not significantly shorten the LOS in infants with acute viral bronchiolitis, compared with nebulized ALB and PLAC. We suggest that hospitalized infants with first-time wheezing, consistent with acute viral bronchiolitis, are best treated with supportive therapies such as oxygen, supplemental fluids, and careful observation.

We thank Natalie Ross (administration) and Isabelle Morin (statistical analyses) for their invaluable help. We acknowledge the cooperation of the Emergency Department, the Department of Pharmacy (Patricia Vanderwruy), the General Pediatric Ward Staff and especially the Bronchiolitis Research Team.

REFERENCES


You can find additional data from this study by logging onto The Journal of Pediatrics Online at www.mosby.com/jpeds.

Fig 1. Flow diagram of patient allocation. *Reason for exclusion: previous wheezing (110), consent declined (43), missed recruitment (42), >12 months, (38), apneic spells/ICU admission (28), >8 hours of therapy pre-enrollment (26), gestational age <34 weeks (17), attending physician refused participation (17), underlying cardiac or pulmonary disease (15), family not fluent in English or French (7), and no reason specified (3).