ORIGINAL ARTICLE

A Multicenter, Randomized, Double-Blind, Controlled Trial of Nebulized Epinephrine in Infants with Acute Bronchiolitis

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ABSTRACT

BACKGROUND

The treatment of infants with bronchiolitis is largely supportive. The role of bronchodilators is controversial. Most studies of the use of bronchodilators have enrolled small numbers of subjects and have examined only short-term outcomes, such as clinical scores.

METHODS

We conducted a randomized, double-blind, controlled trial comparing nebulized single-isomer epinephrine with placebo in 194 infants admitted to four hospitals in Queensland, Australia, with a clinical diagnosis of bronchiolitis. Three 4-ml doses of 1 percent nebulized epinephrine or three 4-ml doses of normal saline were administered at four-hour intervals after hospital admission. Observations were made at admission and just before, 30 minutes after, and 60 minutes after each dose. The primary outcome measures were the length of the hospital stay and the time until the infant was ready for discharge. The secondary outcome measures were the degree of change in the respiratory rate, the heart rate, and the respiratory-effort score and the time that supplemental oxygen was required.

RESULTS

There were no significant overall differences between the groups in the length of the hospital stay (P=0.16) or the time until the infant was ready for discharge (P=0.86). Among infants who required supplemental oxygen and intravenous fluids, the time until the infant was ready for discharge was significantly longer in the epinephrine group than in the placebo group (P=0.02). The need for supplemental oxygen at admission had the greatest influence on the score for severity of illness and strongly predicted the length of the hospital stay and the time until the infant was ready for discharge (P<0.001). There were no significant changes in the respiratory rate, blood pressure, or respiratory-effort scores from before each treatment to after each treatment. The heart rate was significantly increased after each treatment with epinephrine (P=0.02 to P<0.001).

CONCLUSIONS

The use of nebulized epinephrine did not significantly reduce the length of the hospital stay or the time until the infant was ready for discharge among infants admitted to the hospital with bronchiolitis.

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ACUTE VIRAL BRONCHIOLITIS IS THE most common lower respiratory tract infection in the first year of life; approximately 1 percent of healthy infants are hospitalized with this infection annually.[1,2] It is generally a self-limiting condition and is most commonly associated with respiratory syncytial virus infection. It is characterized by bronchiolar obstruction due to edema, with accumulation of mucus and cellular debris.[3] The treatment of infants with bronchiolitis has been largely supportive, with supplemental oxygen, minimal handling of the infant, and the use of intravenous fluids or ventilatory support where necessary. The role of bronchodilators is controversial. The recent Cochrane Review of the use of bronchodilators for bronchiolitis showed short-term improvement in clinical scores, with no improvement in measures of oxygenation or in the rate of hospitalization.[4]

Wohl and Chernick postulated that, since mucosal edema was an important component of airway obstruction in infants with bronchiolitis, a logical approach to therapy might be to use a combined α-adrenergic and β-adrenergic agonist, such as epinephrine.[3] Eleven trials of epinephrine in bronchiolitis have been reported. One was an uncontrolled trial in patients undergoing ventilation.[5] Ten trials were conducted in patients not undergoing ventilation; 6 of the 10 compared epinephrine with albuterol,[6-11] and 4 compared epinephrine with placebo.[12-15] In most studies, epinephrine was administered by nebulizer, although some studies used parenteral administration.[9,14] The doses ranged from 0.5 mg[6] to approximately 8 mg.[11] Most studies measured changes in clinical scores; seven used pulse oximetry[5-9,12,13]; and four measured pulmonary mechanics.[5,10,11,15] Only one study reported the length of the hospital stay[6]; however, that study involved only 30 patients and may have been underpowered. Most studies reported some improvement in short-term outcomes, although the condition of a few patients worsened, as measured by clinical scores,[10] pulmonary mechanics,[5] or oximetric findings[7] after they received epinephrine.

We conducted a large, multicenter, randomized, double-blind, placebo-controlled study to examine the effect of nebulized epinephrine on the length of the hospital stay among infants with bronchiolitis.

METHODS

Infants less than 12 months of age (or less than 12 months of corrected age if they were premature) who were admitted to any of four Queensland, Australia, hospitals (Royal Children's Hospital, Gold Coast Hospital, Caboolture Hospital, and Redcliffe Hospital) between April 2000 and September 2001 with a first episode of wheezing requiring hospitalization and with a clinical diagnosis of bronchiolitis were considered for entry into the study. A clinical diagnosis of bronchiolitis was made if the infant had a history of upper respiratory tract infection and clinical findings consistent with bronchiolitis, including wheezing or wheezing with crackles and respiratory distress with chest recession. Infants with cardiac disease or clinically significant respiratory disease, such as cystic fibrosis, were not eligible, although infants with chronic neonatal lung disease associated with prematurity were included. Infants were excluded if they had received corticosteroids in any form within 24 hours before presentation or had received bronchodilators within 4 hours before presentation. Infants who required ventilatory support before their parents could give consent for their participation in the study were not eligible. After written informed parental consent had been obtained, the infants were randomly assigned to receive three doses of nebulized single-isomer epinephrine or placebo at 4-hour intervals within 24 hours after their admission to the hospital.

Randomization was performed by the pharmacy at the Princess Margaret Hospital in Perth, Australia, which manufactured the treatment packages. Randomization was stratified according to center in blocks of 50 numbers, so that each block comprised 25 patients randomly assigned to epinephrine and 25 to placebo. Two of the smaller hospitals, Caboolture and Redcliffe, were regarded as one center for the purpose of stratification. Each patient was assigned the next sequential number for the particular center. There was one bottle of epinephrine or placebo solution per patient randomly assigned to a treatment group, corresponding to the patient's number. Interim analysis was performed by the study statistician, as requested by the Royal Children's Hospital ethics committee, after the first 50 patients from the Royal Children's Hospital had undergone randomization. The absence of a finding of superiority in the interim analysis was communicated solely to the principal investigator and the ethics committee. Except for the interim analysis, the allocation codes were not opened until the trial was completed.

All children admitted to Royal Children's, Gold Coast, Caboolture, and Redcliffe hospitals with bronchiolitis were treated according to the same

clinical pathway to ensure consistent care and minimize the variability of the results. The length of the hospital stay may have been affected by many administrative and social factors unrelated to the condition of the child. Therefore, we recorded another measure of efficacy: the time until the child was ready for discharge. An infant was considered ready for discharge if he or she had not received supplemental oxygen for 10 hours, had minimal or no chest recession, and was feeding adequately, without the need for intravenous fluids. The clinical pathway included guidelines for the use and termination of supplemental oxygen and the use of intravenous fluids, although the treating physicians were free to use supplemental oxygen or intravenous fluids as they thought appropriate. The criterion for supplemental oxygen was less than 94 percent oxygen saturation or any combination of clinically significant respiratory distress, a respiratory rate above 60 per minute, and difficulty in feeding. The use of supplemental oxygen was terminated when the oxygen saturation was consistently above 93 percent or when the infant's condition had been stable for four hours and he or she was starting to tolerate oral feeding.

The guidelines suggested that infants should receive intravenous fluids rather than oral feeding if supplemental oxygen was required and the respiratory rate was above 60 per minute, or if oral feeding was deemed inadequate. Comfort feeding was allowed. The use of intravenous fluids was terminated when the infant was able to tolerate oral feeding. Data were also collected on variations in the clinical pathway, including the use of other drugs during hospitalization. Data on readmission to the hospital in the month after discharge were also collected.

Each infant was assigned one amber bottle containing 15 ml of clear, colorless solution with an odor of chlorobutanol, containing either epinephrine (epinephrine acid tartrate, 1 percent, with sodium metabisulfite and vehicle), or vehicle (chlorobutanol, edetate disodium, sodium chloride, and purified water); the contents were sufficient for three doses of 4 ml, with some margin for spillage.

A nasopharyngeal-aspiration sample was obtained routinely from all patients for detection of respiratory syncytial virus. The admitting medical officer and nurse recorded detailed clinical histories in the clinical pathway, including the duration of symptoms before presentation at the hospital, the medical history, the infant's ability to feed, current and previous medications, immunization record, parental smoking history, and family history of atopy. Observations at admission included respiratory rate and heart rate while the infant was quiet, temperature, respiratory effort, oxygen saturation while breathing room air, presence or absence of wheezing or crackles on auscultation of the chest, and level of hydration. The respiratory rate, measured over a period of 30 seconds, was scored by comparison with data on age-matched normal infants.[16] Each infant's condition was classified as mild, moderate, or severe according to a severity score calculated from the oxygen saturation, respiratory rate, and respiratory effort observed at admission (Table 1).

Epinephrine and placebo were administered by means of standard hospital jet nebulizers through a firmly applied face mask with an oxygen flow of 6 liters per minute. MicroMist (Hudson RCI) with an Aerflo mask (Maersq Medical) was used at Caboolture Hospital, Misty-Neb AirLife (Baxter) with an Aerflo mask at Redcliffe Hospital, Sidestream Medic-Aid (Niche Medical UK) with a Medic-Aid pediatric mask at Gold Coast Hospital, and MicroMist with an Aerosol Mask (Hudson RCI) at Royal Chil-

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Table 1. Calculation of the Severity Score.

Respiratory-effort score

The nurse examined the patient for intercostal recession, subcostal recession, substernal recession, tracheal tug, and nasal flaring and assigned a score of 0 (not present), 1 (mild to moderate), or 2 (severe) for each factor. Each score was then multiplied by a weighting factor, as follows: intercostal recession (×1), subcostal recession (×1), substernal recession (×1), tracheal tug (×1.5), and nasal flaring (×1.5). The weighted scores were then totaled to obtain a score for respiratory effort. Finally, infants with respiratory-effort scores of 0 to 4.9 were given a severity score of 1 (mild); those with respiratory-effort scores of 5.0 to 8.9 were given a score of 2 (moderate); and those with respiratory-effort scores of 9.0 to 12.0 were given a score of 3 (severe).

Oxygen saturation breathing ambient air

The infants received scores of 0, 1, or 2 for oxygen-saturation values of 95 to 100 percent, 90 to 94 percent, and less than 90 percent, respectively.

Respiratory rate compared with that of healthy infants of the same age

Those whose rates were within 2 SD of the mean for their age received a score of 0; those whose rates were 2 to 3 SD above or below the mean for their age received a score of 1; and those whose rates were more than 3 SD from the mean for their age received a score of 2.

Overall severity score

The above three scores were totaled for each infant, and the infant's condition was classified as mild (total score less than 2), moderate (total score 2 to 3), or severe (total score more than 3).

dren's Hospital. The same types of nebulizer bowls and masks were used throughout the study at each hospital. The nursing staff recorded the respiratory and heart rates while the patient was quiet, supplemental oxygen requirements, oxygen saturation, respiratory effort (scoring each component as mild, moderate, or severe), and blood pressure just before and 30 and 60 minutes after the delivery of the drug.

The two primary outcomes were the length of the hospital stay and the time until the infant was ready for discharge. The secondary outcomes were changes in the components of the clinical scores before and after nebulization therapy and the time that supplemental oxygen was required.

ETHICS

The study was approved by the ethics committees of all four centers. Written informed consent was obtained for each infant from a parent.

ESTIMATE OF SAMPLE SIZE

Calculation of power was difficult, because no accurate data were available for this group of patients on the standard deviation of the length of the hospital stay or the length of time receiving supplemental oxygen. We therefore specified that we aimed to detect a difference between the two groups of half a standard deviation in the length of the hospital stay and the time until the infant was ready for discharge at the 1 percent significance level for a two-sided test with 85 percent power; this would require 200 infants, with 100 infants in each group.

STATISTICAL ANALYSIS

The data from all randomized patients were analyzed on an intention-to-treat basis. The differences between the treatment groups in the characteristics of the patients were assessed by Fisher's exact test and the Mann–Whitney test with exact probabilities. Between-group comparisons of the length of the hospital stay, the time until the infant was ready for discharge, and the length of time receiving supplemental oxygen were performed by analysis of variance after appropriate logarithmic transformation to correct for skewness. Time receiving oxygen was analyzed as a conditional variable, since not all infants required oxygen. The analysis was performed with SPSS software (standard version 10). One-way analysis of variance was used for a simple comparison between the two randomized groups. Means and 95 percent confidence intervals

were back-transformed from log to linear scales for presentation. The treatment differences and their confidence intervals were also back-transformed from log to linear scales to calculate the ratio of the results with epinephrine to the results with placebo. To adjust this comparison, the effects of covariates were screened with use of general linear modeling. The covariates, which were assessed at admission, before randomization, were the hospital at which the infant was treated, the severity score, and the use or nonuse of supplemental oxygen, with or without the use of intravenous fluids. Both the use of supplemental oxygen, with or without the use of intravenous fluids, and its interaction with the treatment group were significant (P<0.05), but other covariates and their interactions were not significant. Hence the treatment comparison was also performed separately according to the use or nonuse of supplemental oxygen and intravenous fluids, with pooled variance for each comparison. There was no interaction between the severity score and treatment, nor was severity a significant covariate when the use of supplementary oxygen, with or without the use of intravenous fluids, was included in the model. All reported P values are two-sided.

RESULTS

A total of 194 infants were assigned to treatment: 99 to epinephrine and 95 to placebo. There were no significant differences between the groups at randomization in terms of demographic variables, the proportion of infants requiring supplemental oxygen or intravenous fluids, or the proportion of infants whose nasopharyngeal aspirate was positive for respiratory syncytial virus (Table 2). There were no significant differences at admission between the groups in the duration of wheezing (P=0.16) or the duration of coryza (P=0.35) (Table 2).

PRIMARY END POINTS

Treatment with epinephrine had no significant effect on the length of the hospital stay (P=0.16) or the time until the infant was ready for discharge (P=0.86). The ratio of the length of the hospital stay in the epinephrine group to that in the placebo group was 0.85 (95 percent confidence interval, 0.67 to 1.07). The ratio of the time until ready for discharge in the epinephrine group to that in the placebo group was 0.98 (95 percent confidence interval, 0.74 to 1.29) (Table 3). The length of the hospital stay for the epinephrine group ranged from

10 to 443 hours, with an interquartile range of 26 to 116 hours. The range for the placebo group was 13 to 438 hours, with an interquartile range of 42 to 111 hours. In the epinephrine group, the time until the infant was ready for discharge ranged from 7 to 398 hours, with an interquartile range of 21 to 101 hours. The range in the placebo group was 8 to 380 hours, with an interquartile range of 21 to 95 hours. The need for supplemental oxygen, with or without intravenous fluids, had by far the greatest influence on the severity-of-disease ranking (P<0.001) and strongly predicted the length of the hospital stay (Fig. 1). Among infants requiring both supplemental oxygen and intravenous fluids, the time until the infant was ready for discharge in the epinephrine group (135.9 hours; 95 percent confidence interval, 96.6 to 191.3) was significantly longer than that in the placebo group (80.2 hours; 95 percent confidence interval, 62.0 to 103.5; P= 0.02). The differences between the epinephrine and placebo groups in the length of the hospital stay and the time until ready for discharge were not significant for infants who received no oxygen or oxygen without intravenous fluids (P=0.06 to P=0.39) (Table 3). The difference between the length of the hospital stay and the time until the infant was ready for discharge was significantly greater in the placebo group than in the epinephrine group (P=0.03).

SECONDARY END POINTS

There was no significant difference between the groups in the time receiving supplemental oxygen (Table 3). Seven infants (3.6 percent) required admission to the intensive care unit, and three (1.5 percent) required ventilatory support. There were no significant differences between the groups in the proportions requiring intensive care (P=0.23) or ventilatory support (P=0.08).

Three patients were readmitted to the hospital within one month after discharge (two in the placebo group and one in the epinephrine group). Fourteen infants did not receive all three doses of nebulized epinephrine or placebo (10 in the epinephrine group and 4 in the placebo group, P=0.11). Three infants in the placebo group received antibiotics, as did one in the epinephrine group. No infants received steroid therapy, and two in the placebo group were treated with bronchodilators other than epinephrine when their condition failed to improve.

Epinephrine had a significant effect on the heart rate (Fig. 2). Sixty minutes after the last nebulization treatment, the mean heart rate was 151 per minute

Table 2. Demographic Characteristics of the Infants at Admission to the Hospital.			
Characteristic	Epinephrine (N=99)	Placebo (N=95)	P Value
Mean (±SD) age — mo	4.52±3.01	4.35±2.95	0.70
Sex — M/F	60/39	61/34	0.66
Parental smoking — no. (%)			0.50
Both parents	22 (22.2)	19 (20.0)	
One parent	30 (30.3)	26 (27.4)	
Neither parent	47 (47.5)	50 (52.6)	
Duration of coryza at admission — no. (%)*			0.35
No coryza	13 (13.1)	15 (15.8)	
<3 days	30 (30.3)	33 (34.7)	
3–6 days	44 (44.4)	37 (38.9)	
>6 days	12 (12.1)	10 (10.5)	
Duration of wheezing at admission — no. (%)*			0.16
No wheezing	41 (41.4)	42 (44.2)	
<3 days	31 (31.3)	42 (44.2)	
3–6 days	21 (21.2)	7 (7.4)	
>6 days	6 (6.1)	4 (4.2)	
Severity of condition — no. (%)			0.73
Mild	50 (50.5)	55 (57.9)	
Moderate	31 (31.3)	16 (16.8)	
Severe	18 (18.2)	24 (25.3)	
Positive for respiratory syncytial virus — no. (%)	70 (70.7)	59 (62.1)	0.23
Premature birth — no. (%)	13 (13.1)	15 (15.8)	0.68
Gestation — wk			
Median	35	35	
Range	27–36	25–36	
Supplementary oxygen and intravenous feeding — no. (%)			0.20
No oxygen	37 (37.4)	33 (34.7)	
Oxygen only	49 (49.5)	38 (40.0)	
Oxygen and intravenous feeding	13 (13.1)	24 (25.3)	

* The data were obtained by parental report.

in the epinephrine group (95 percent confidence interval, 147 to 156), as compared with 138 per minute in the placebo group (95 percent confidence interval, 134 to 142; P<0.001). In general, the respiratory rate 30 minutes after treatment tended to be slightly higher (by about two breaths per minute) in the epinephrine group than in the placebo group, although the difference did not reach significance (P=0.10 to P=0.68). There was little change in the blood pressure of infants in the placebo group before and after treatment. In the epinephrine group, there was an increase of about 5 mm Hg in both systolic and diastolic blood pressure 30 minutes after treatment, which did not reach significance (P=0.06

Table 3. Length of the Hospital Stay, Time until the Infant Was Ready for Discharge, and Time Supplemental Oxygen Was Required, According to the Use or Nonuse of Supplemental Oxygen and Intravenous Fluids.

Variable	Epinephrine (N=99)	Placebo (N=95)	Ratio of Means of Epinephrine and Placebo Groups	P Value
	mean (95% confidence interval)			
Length of hospital stay (hr)				
Overall	58.8 (49.4–70.0)	69.5 (59.3–81.4)	0.85 (0.67–1.07)	0.16
No oxygen	25.8 (21.4–31.0)	33.5 (27.5–40.8)	0.77 (0.59–1.01)	0.06
Oxygen only	85.9 (73.1–100.9)	98.0 (81.6–117.7)	0.88 (0.69–1.12)	0.29
Oxygen and intravenous fluids	147.4 (107.9–201.5)	109.6 (87.1–138.0)	1.34 (0.91–1.98)	0.14
Time until ready for discharge (hr)				
Overall	46.5 (38.3–56.5)	47.7 (39.0–58.3)	0.98 (0.74–1.29)	0.86
No oxygen	18.6 (15.2–22.9)	16.3 (13.1–20.3)	1.14 (0.85–1.55)	0.39
Oxygen only	68.5 (57.5–81.7)	83.5 (68.4–102.0)	0.82 (0.63–1.07)	0.15
Oxygen and intravenous fluids	135.9 (96.6–191.3)	80.2 (62.0–103.5)	1.70 (1.11–2.60)	0.02
Time supplemental oxygen required (hr)				
Overall	54.0 (40.9–71.2)	58.8 (46.8–73.8)	0.92 (0.64–1.31)	0.64
Oxygen only	43.6 (33.2–57.2)	56.1 (41.2–76.4)	0.78 (0.52–1.17)	0.22
Oxygen and intravenous fluids	121.0 (71.4–205.2)	63.2 (42.9–93.3)	1.91 (0.99–3.68)	0.06

to P=0.83). There was no significant difference between the groups in the change in the respiratory-effort score from before to 60 minutes after each treatment (P=0.18 to P=0.76), although 30 minutes after the first treatment the epinephrine group had a lower respiratory-effort score than the placebo group (P=0.04) (Fig. 3). However, the epinephrine group had slightly lower respiratory-effort scores 60 minutes after the final nebulization than the placebo group (2.44 [95 percent confidence interval, 1.97 to 2.92] vs. 3.35 [95 percent confidence interval, 2.78 to 3.91], P=0.02).

Univariate analysis of the length of the hospital stay and the time receiving supplemental oxygen showed no significant differences between the responses to epinephrine at the various hospitals (P=0.31 and P=0.66, respectively). Among patients receiving epinephrine, there was no significant difference in the length of hospital stay between those who were and those who were not positive for respiratory syncytial virus (P=0.11), or between those with a first-degree relative who had a history of asthma, eczema, or hay fever and those who did not have such a family history (P=0.94).
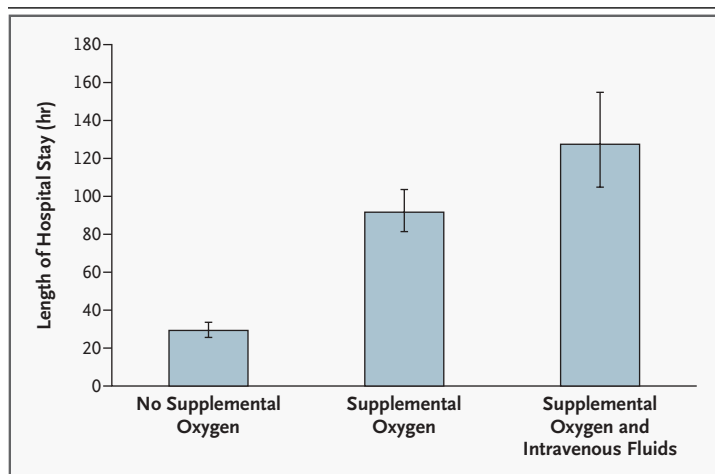
DISCUSSION

The role of bronchodilators in acute bronchiolitis is controversial, and the interpretation of many studies is complicated by the use of different definitions of bronchiolitis, some of which apply the diagnosis to young children with recurrent wheezing illness that is more likely to be due to asthma. In addition, previous studies have had small numbers of subjects, thus increasing the risks of a type I error. This large, randomized, double-blind, controlled trial of an inhaled bronchodilator with both α-adrenergic and β-adrenergic effects in infants with acute bronchiolitis has clearly demonstrated that bronchodilators do not produce a clinically relevant improvement in clinical status or reduce the length
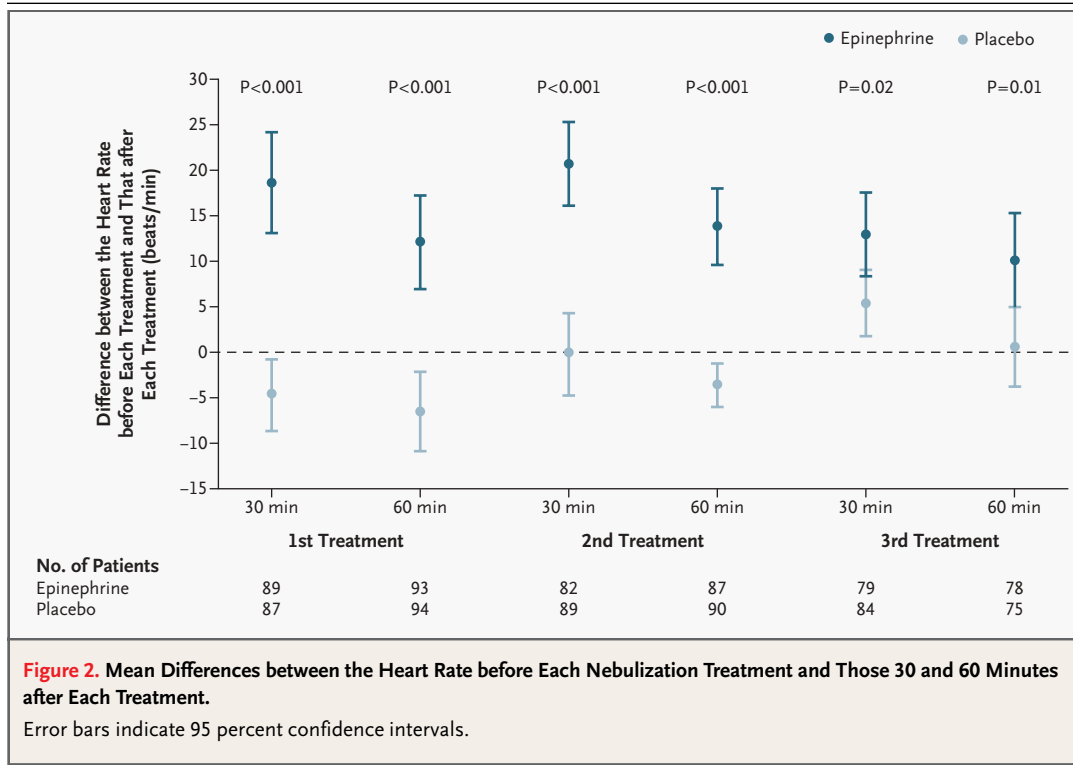

Figure 1. Mean Length of the Hospital Stay According to the Need for Supplemental Oxygen and Intravenous Fluids at Admission.
Error bars indicate 95 percent confidence intervals.

Figure 2. Mean Differences between the Heart Rate before Each Nebulization Treatment and Those 30 and 60 Minutes after Each Treatment.

Error bars indicate 95 percent confidence intervals.

of the hospital stay in infants less than 12 months of age with acute bronchiolitis.

Previous studies have found an improved short-term clinical score after administration of an inhaled bronchodilator. A substantial effect on the length of the hospital stay and the time until the infant is ready for discharge would require a sustained clinical improvement. It could be argued that bronchodilator therapy, particularly with a short-acting bronchodilator, would not be likely to affect longer-term outcomes unless therapy was given frequently or had some beneficial effect on the underlying pathophysiology. The α-adrenergic effects of nebulized epinephrine might reduce airway edema, which is thought to have a role in the pathophysiology of acute bronchiolitis. Transient reductions in edema might improve pulmonary mechanics and clearance of secretions, which could possibly have a longer-lasting benefit. We thought that if nebulized epinephrine resulted in any significant clinical improvement, albeit transient, it should be apparent from our observations before and after the administration of the three doses over the nine hours of repeated observations. No consistent statistically significant change in the respiratory rate or respiratory-effort score was found from before each treat-ment to after each treatment, although the infants in the epinephrine group did have a lower respiratory-effort score after all three treatments. The improvement in the respiratory-effort score therefore occurred between treatments rather than during the observation period for each treatment. Thus, either the improvement occurred several hours after the administration of epinephrine or it was not related to the treatment at all. Although the respiratory-effort score was significantly lower in the epinephrine group after the three treatments, the difference between the groups was small and clinically trivial, and it was not associated with a shorter time to readiness for discharge or a shorter hospital stay.

The randomization was not stratified according to the severity of illness. More infants with moderately severe illness were assigned to epinephrine than to placebo, although the difference did not reach statistical significance. This difference could theoretically have moderated the effect of epinephrine in this group. However, more infants in the placebo group than in the epinephrine group required both intravenous fluids and supplemental oxygen (although the difference was not significant), a difference that could have increased the chances of finding a significant difference between the groups
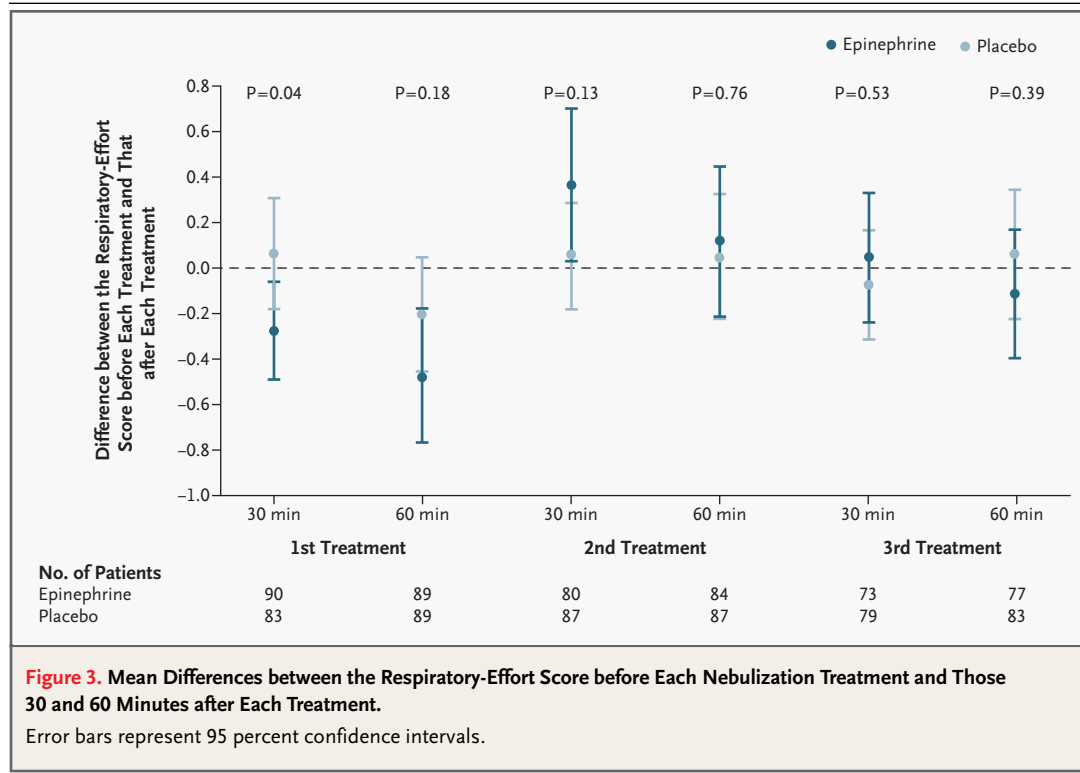
Figure 3. Mean Differences between the Respiratory-Effort Score before Each Nebulization Treatment and Those 30 and 60 Minutes after Each Treatment.

Error bars represent 95 percent confidence intervals.

in the length of the hospital stay and time until the infant was ready for discharge.

Three different nebulizer systems were used in this trial, all of which had similar minimal residual volumes, with a respirable output under 5 μm ranging from 76 to 85 percent. There were no significant differences between hospitals in the response to epinephrine or in the change in heart rate, suggesting that enough epinephrine was administered at each site to produce a measurable physiological change. This would make it less likely that the lack of benefit with nebulized epinephrine was due to differences in the amounts administered by different nebulizer systems.

Some trials of nebulized epinephrine have used racemic epinephrine to reduce potential cardiac effects, and an increase in heart rate has not been consistently reported.[10,12,13] In a small study, Kristjansson et al. found a small, clinically trivial increase in systolic blood pressure immediately after and 45 minutes after the administration of nebulized epinephrine but not 15, 30, or 60 minutes after the drug was given.[12] We report here a small but statistically significant increase in the heart rate, which could theoretically increase oxygen-utilization costs in vulnerable infants. Newth et al. described an in-

crease in oxygen utilization in rhesus monkeys breathing β_2-agonists that was blocked by the use of propranolol, suggesting a β-receptor–mediated mechanism.[17] Among our patients assigned to epinephrine who required both supplemental oxygen and intravenous fluids, there was a significant increase in the time until the infant was ready for discharge and a trend toward an increase in the duration of oxygen supplementation. Infants who required both supplemental oxygen and intravenous fluids would be the most vulnerable and sickest patients, and increased oxygen utilization could lead to prolonged use of supplemental oxygen and an increase in the time until the infant was ready for discharge.

The difference between the length of the hospital stay and the time until the infant was ready for discharge was more than twice as great in the placebo group as in the epinephrine group for those requiring no supplemental oxygen and for those requiring both supplemental oxygen and intravenous fluids. This may explain the trend toward a slightly shorter hospital stay among infants in the epinephrine group who did not require supplemental oxygen than among infants in the placebo group who did not require supplemental oxygen, since there

was no such trend in the time until the infant was ready for discharge.

Many health care professionals treat bronchiolitis with a bronchodilator just in case it is a first manifestation of asthma. Although we could not determine which infants in this study would later have asthma, we did find that a history of asthma, eczema, or hay fever in a first-degree relative did not affect the response to nebulized epinephrine. This would suggest that bronchodilators are not effective, even in children with acute bronchiolitis who are at higher-than-average risk for asthma.

The need for supplemental oxygen, based on the patient's oxygen saturation while breathing room air at admission, was highly predictive of the length of the hospital stay. Similarly, oxygen saturation on admission with acute asthma is highly predictive of the severity of asthma.[18] Oxygen saturation measurements are usually performed in all infants admitted to the hospital with acute bronchiolitis and could therefore easily be used for planning appropriate staffing and bed requirements for pediatric wards.

This trial mirrors the reality of clinical practice in both tertiary care and district hospitals, and our results are therefore applicable to the majority of hospitalized infants with acute bronchiolitis. Bronchodilators are widely used in many countries for infants with bronchiolitis. Approximately 68 to 96 percent of infants with bronchiolitis are treated with bronchodilators at tertiary pediatric centers in Canada.[19,20] In a European survey of 88 pediatric centers, 54 centers reported using bronchodilators in all patients with bronchiolitis, and 15 centers reported using bronchodilators only in high-risk patients.[21] In a survey of Australian pediatricians, 88 percent of respondents reported that they used bronchodilators in some infants with bronchiolitis, and 21 percent that they used epinephrine in such infants.[22] Because there have been no previous large, randomized, controlled trials, the use of bronchodilators for bronchiolitis has been controversial, with multiple small studies reporting different outcomes with different bronchodilators. The evidence from this trial points clearly to a lack of benefit, in either short-term or long-term clinically relevant outcomes, of nebulized epinephrine in infants hospitalized with acute bronchiolitis.

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