

Randomized controlled trial of nebulized adrenaline in acute bronchiolitis

Hariprakash S, Alexander J, Carroll W, Ramesh P, Randell T, Turnbull F, Lenney W. Randomized controlled trial of nebulized adrenaline in acute bronchiolitis.

Pediatr Allergy Immunol 2003; 14: 134–139. © 2003 Blackwell Munksgaard

Use of both L-epinephrine and racemic epinephrine (adrenaline) has improved clinical symptoms and composite respiratory scores in acute bronchiolitis. The objective of this randomized double-blind placebo-controlled study was to assess whether there was sufficient improvement in clinical state to reduce hospital admissions. Seventy-five infants aged 1 month to 1 year with a clinical diagnosis of acute bronchiolitis were treated with either 2 ml of 1:1000 nebulized adrenaline or 2 ml of nebulized normal saline administered after baseline assessment and 30 min later. Clinical respiratory parameters were recorded at 15-min intervals for a period of 2 h following the baseline assessment. Admission to hospital was the primary end-point and changes in respiratory parameters were secondary end-points. Fifty percent (19/38) of infants treated with adrenaline were discharged home compared with 38 percent (14/37) of those treated with saline. This 12 percent reduction in rate of admission is not statistically significant (95% CI of difference: –10% to 35%). There was no difference between treated and placebo groups in respiratory rate, oxygen saturation, heart rate or a composite respiratory distress score at 30, 60 or 120 min post-treatment. In this study, nebulized epinephrine did not confer a significant advantage over nebulized saline in the emergency room treatment of acute bronchiolitis.

**Suriyanarayanapillai Hariprakash,
John Alexander, Will Carroll,
Pavanasam Ramesh, Tabitha
Randell, Frances Turnbull and Warren
Lenney**

Department of Paediatrics, North Staffordshire
Hospital NHS Trust, Stoke-on-Trent, United Kingdom

Key words: bronchiolitis; hospital admission;
nebulized adrenaline

Dr J. Alexander, Paediatric Intensive Care Unit, City
General Hospital, Stoke-on-Trent ST4 6QG, United
Kingdom
Tel.: +44 1782 552 751
Fax: +44 1782 553 831
E-mail: jalexander@rocketmail.com

Accepted 24 June 2002

Acute viral bronchiolitis (AVB) is the most common lower respiratory tract infection in infants and 1–2% of all infants are hospitalized due to this condition (1). Respiratory syncytial virus (RSV) is the causative organism in approximately 75% and AVB occurs typically in epidemic form between November and March in the Northern Hemisphere.

AVB is an inflammatory disease of the small airways. Mucosal and submucosal edema, necrosis and desquamation of ciliated epithelial cells and proliferation of non-ciliated cells are the principal pathophysiological findings (2, 3). There is increased mucus secretion and impaired secretion clearance. Eventually small airway obstruction, gas trapping and impaired gas exchange ensues.

In the majority of infants, AVB disease is mainly confined to the upper airways, with a mild self-limiting illness that can be managed at home. Children needing hospital treatment are usually

admitted because of progressive respiratory distress, increased work of breathing or poor feeding. The mean duration of hospital stay is about 3 days (4).

Studies of interventions to provide symptomatic relief have failed to demonstrate clear benefit. Treatment with ipratropium bromide has not improved respiratory rate, heart rate or oxygen saturation (SaO₂) (5, 6). Treatment with β_2 agonists has produced conflicting results (7–10), with some favoring treatment (10–12) and others showing no benefit over placebo (13, 14). Reduction in SaO₂ when using nebulized salbutamol suggests that it might even be deleterious (6, 13).

A meta-analysis of bronchodilator therapy showed modest short-term clinical improvement in mild-to-moderate disease but showed no effect on hospitalization (15). SaO₂ results were too varied to allow pooling of results. A further meta-analysis showed β_2 agonists were not

effective in improving clinical symptoms or reducing hospitalization (16).

Alpha-adrenergic stimulants such as phenylephrine do not improve lung function or symptoms (17). Oral and nebulized corticosteroids and parenteral RSV immunoglobulins have not produced significant symptom improvement, reduction in hospital admissions rates or reduced length of hospital stay (18–21).

Adrenaline (epinephrine) has both alpha- and beta-adrenergic receptor agonist activities. The alpha-receptor activity reduces capillary and post-capillary microvascular leakage, thereby reducing bronchiolar edema (22). The beta-receptor activity causes bronchiolar dilatation. Nebulized racemic epinephrine has shown clinical improvement and a reduced hospital admission rate in some children with bronchiolitis and in some with viral wheeze (23–25). One study has suggested intramuscular racemic epinephrine is effective (26). However, racemic epinephrine is not available in the UK and intramuscular injections are not a commonly used treatment in children with bronchiolitis.

A study comparing nebulized non-racemic adrenaline with nebulized salbutamol showed significant improvement in SaO_2 at 60 min, reduction in heart rate at 90 min and a greater rate of discharge from hospital in children treated with adrenaline. Eight-one percent of children in the salbutamol group were admitted compared with only 33% in the adrenaline group (27). The purpose of this study was to examine the effect of nebulized adrenaline on the need for hospital admission in a district hospital in the United Kingdom.

Methods

Study setting

The study was carried out in the pediatric admission unit of the North Staffordshire Hospital, Stoke-on-Trent, UK. The unit is open from 08.00 to 22.00 hours and staffed by a junior pediatrician, a senior pediatrician of registrar level and experienced nursing staff. Children referred by general practitioners and from the main Accident and Emergency Department are assessed and observed here before admission or discharge home. Children referred between 22.00 and 08.00 hours are few in number and usually assessed directly on the ward. For practical reasons, these children were not included in the study.

Selection of patients

Inclusion. This study was conducted from November 1998 to January 2000. No patients were recruited from March 1999 to October 1999. Infants, aged 1 month to 1 year of age, presenting to the admitting unit with clinical features compatible with a diagnosis of bronchiolitis were eligible. For the purpose of this study, clinical bronchiolitis was defined as the presence of inspiratory crackles in an infant with an otherwise predominantly upper respiratory tract illness.

Exclusion. Infants who had very mild illness [Respiratory Distress Assessment Instrument (RDAI) score < 3], who were born extremely preterm (< 30 weeks), who had chronic cardio-pulmonary disease, who were immunosuppressed or who had received steroids (oral/parenteral/inhaled) within the previous 24 h were excluded. Children referred after 22.00 hours and before 08.00 hours and those who required support other than O_2 were also excluded.

Consent

The study was approved by the local research ethics committee and informed consent was obtained from at least one parent or carer.

Study design

Eligible children were referred to one of four specialist registrars by the clinical team. If they satisfied the entry criteria and parents gave informed consent, they were randomly assigned to receive two doses of nebulized adrenaline 2 ml of 1:1000 solution diluted to 5 ml with 0.9% saline or two doses of 5 ml of 0.9% saline. The pharmacy department, using sealed envelopes according to a random numbered sequence, performed the randomization. Both medicines were packaged in identical syringes identified only by the study number. Nebulizations were administered immediately after baseline assessment and 30 min later, using a nebulizer and face mask (Sidestream Medic Aid System 22, Bognor Regis, UK) driven by continuous flow oxygen at 6 l/min. Secondary outcome variables were measured every 15 min after the first nebulized treatment by the research registrar. The RDAI score, a measure of illness severity, has been validated in bronchiolitis (26) and was chosen as a composite variable. Respiratory rate and heart rate were counted manually and SaO_2 measured

Table 1. Summary of demographic characteristics

Demographic characteristic	Epinephrine (n = 38)	Placebo (n = 36)*	p
Mean age, months (range)	4.95 (0.95–11.01)	5.25 (1.38–11.41)	0.66
Mean birth weight, kg (range)	3.35 (2.15–4.40)	3.15 (1.52–4.44)	0.11
Gestation, weeks (range)	39.1 (35–42)	38.4 (30–42)	0.23
Admission to neonatal unit soon after birth (%)	2 (5.2%)	4 (11.1%)	0.36
Ventilatory support soon after birth (%)	0	2 (5%)	0.14
Oxygen therapy soon after birth (%)	2 (5.2%)	4 (11.1%)	0.36
Family history of atopy (%)	29 (76.3%)	31 (83.7%)	0.42
Parental smoking (%)	22 (57.8%)	21 (58.3%)	0.97

*Demographic details of one child from placebo not available.

from either a finger or a toe using a pulse oximeter (Nellcor Inc., Hayward, CA, USA). Medical and nursing staff monitored the children throughout the study period and were free to intervene or withdraw them from the study if clinical deterioration or adverse events occurred. After 2 h, a middle grade pediatrician, who was not one of the research registrars, assessed the infants for admission or discharge. The department has a well-established guideline for the management of acute bronchiolitis and patients are admitted to the ward if they have an oxygen saturation of less than 92% in air, if they are lethargic or if they are unable to feed due to respiratory distress.

Outcome measures/statistics

The primary outcome was admission to hospital after 2 h. Based on our departmental audit showing a 66% admission rate, we calculated that 35 infants in each arm of study would provide an 80% power and alpha of 0.5 to detect a 50% reduction in admission. The 50% reduction was chosen to reflect the magnitude of benefit demonstrated in the study by Menon et al. (27).

Secondary outcomes were reductions in the RDAI score, respiratory rate and the heart rate and an increase in SaO₂. Any adverse events or side-effects were also recorded.

Continuous variables were compared between the two groups using Student's *t*-test and we used the chi-square test to compare ordinal variables.

Results

Patient characteristics

During the first winter (November 1998–January 1999), 85 infants were referred to the trial, 42 of whom entered the study. Of the 43 infants not

included, 10 did not consent to the study, 10 did not meet the RDAI criteria (>3), 3 had the diagnosis of bronchiolitis revised, 2 were too unwell to be included, 5 were inappropriate referrals and miscellaneous organizational factors were involved in the remaining 13. Thirty-three infants were recruited during the second winter, giving a total of 75 infants recruited to the trial. No data were collected on infants where consent was declined or those who were not invited to participate in the study. Thirty-eight infants received nebulized adrenaline and 37 received placebo. There was no difference between the groups in demographic characteristics, known risk factors for severe disease (Table 1), or in baseline physiological measurements.

Main outcome

Fifty percent of the adrenaline group (19/38) and 62 percent of the placebo group (23/37) were admitted to hospital for further treatment. The 12 percent difference between groups was not statistically significant (95% CI of difference = –11% to 35%).

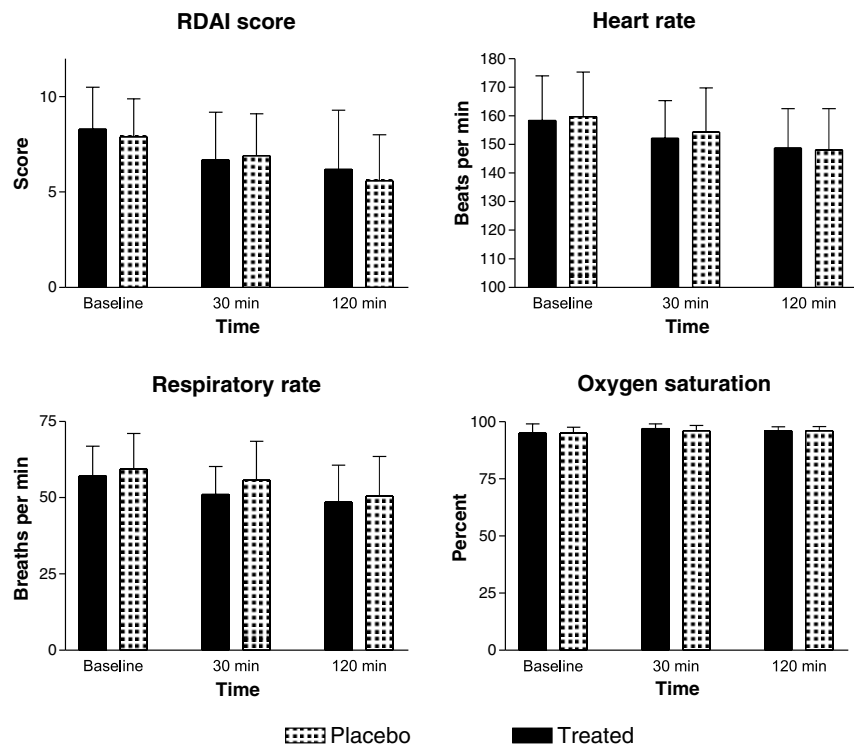
Secondary outcomes

There was no difference between the groups in RDAI scores, respiratory rate, heart rate or SaO₂ at 30 min or 120 min after the nebulizers (Fig. 1). In the study population as a whole, there was a mean reduction in RDAI score of three in children discharged home compared with one in children admitted to hospital.

Adverse effects

There was no pallor, tachycardia, vomiting or arrhythmias in either the adrenaline or the placebo group. No infant was withdrawn from the trial due to side-effects or clinical deterioration.

Fig. 1. Baseline, 30 and 120 min comparison of secondary outcome measures (mean, SD). There was no statistically significant difference between treated and placebo groups in any of the variables at any point in time.



Discussion

The onset of winter each year heralds the bronchiolitis season and, with it, a sharp increase in the admission rates to most pediatric wards. Although the illness is self-limiting and the outcome almost always satisfactory, a high proportion of children still require hospital admission for further treatment. Clinical features and pathophysiological findings clearly indicate that this is a disease of the small airways resulting in airway narrowing, but the use of bronchodilators in the treatment of this condition has only shown transient benefit that is probably not clinically relevant.

Our results show no statistically significant difference in admission rate between nebulized adrenaline and nebulized saline usage. There were no significant differences in respiratory rate, heart rate, RDAI scores and SaO_2 values at baseline at 30 min and at 2 h between the groups. These findings differ from those of Menon et al. (27), and from the studies using nebulized racemic epinephrine in children with bronchiolitis (23, 25, 26).

There were no major differences in the demographic characteristics or other clinical variables between our cohort and those in the Canadian study (27). However, there is a difference in the dose of adrenaline used. Menon et al. used 3 mg of epinephrine on all patients, having calculated this from the maximum dose of racemic epinephrine

used in previous clinical trials of bronchiolitis or croup (25, 28). The dose of racemic adrenaline was taken from the following scale based on body weight used by Kristjansson et al. in 1993: 0.1 mg/kg < 5 kg; 0.15 mg/kg in 5–6.9 kg, 0.2 mg/kg in 7–9.9 kg, and 0.25 mg/kg in > 10 kg infants. Wennergren (25) used nebulized racemic epinephrine in doses of 0.45 mg/kg and 0.9 mg/kg in children with wheezy bronchitis. There seems no agreement on optimal nebulized dose of either racemic or non-racemic adrenaline. We considered 2 mg would be appropriate, as it would be slightly high for a 1-month-old infant but a good therapeutic dose for a 1 year old. Post hoc analysis of our data looking only at infants less than 2 months of age showed no difference in outcome, suggesting that a higher dose was unlikely to have made any significant difference.

We used two nebulizations at 30-min intervals and believe that more nebulizations were unlikely to have made a significant difference to our primary outcome. Moreover, there is evidence to suggest that multiple doses of nebulized racemic adrenaline can be deleterious (29).

Menon concluded that nebulized adrenaline was superior to salbutamol as 33% of children in the adrenaline group were admitted compared with 81% in the salbutamol group (27). It is possible that salbutamol could have made the children worse through reflex bronchoconstriction,

leading to the rather high admission rate in the controls. There was also a statistically significant improvement in SaO_2 , reduction in heart rate at 90 min and faster rate of hospital discharge. In our study, there was a significant reduction in heart rate, respiratory rate and RDAI score and improvement in oxygen saturations over time but this was equal in both groups. This could be accounted for by the supportive care with frequent nasopharyngeal suctioning and possibly the humidifying effect of nebulized solutions along with supplemental oxygen. It is possible that nebulized saline, by simply liquefying the viscid secretions, renders a beneficial effect.

All eligible infants presenting with clinical bronchiolitis were included in our study irrespective of RSV status. Screening for RSV from nasopharyngeal aspirate samples was routine practice in our hospital during the study period. The samples were sent to the laboratory and the results from a rapid enzyme-linked immunosorbent assay (ELISA) test were available later that day to enable cohorting of children who were RSV positive. Samples negative on the rapid ELISA test were tested by immunofluorescence and viral culture. We did not include RSV status as one of our entry criteria as the study was conducted in the assessment unit and the results of RSV status would not be immediately available. However, retrospective analysis of data showed that the proportion of children who were RSV positive were similar [18/38 (47.4%) in the adrenaline and 18/37 (48.6%) in the saline group]. No other pathogens were identified. This is a low rate of pathogen isolation and may reflect problems in obtaining good nasopharyngeal aspirate samples.

Reynolds and Cooke wrote in 1963: 'oxygen is vitally important in bronchiolitis: there is little evidence that any other treatment is useful'. Our study has added little to that statement and based on our results we conclude that the use of nebulized adrenaline did not reduce hospital admissions and did not improve clinical symptoms in our infants with bronchiolitis.

References

- McKENZIE S. Respiratory tract infections. In: CAMPBELL AGM, MCINTOSH N, eds. *Forfar and Arneil's Textbook of Paediatrics*. Edinburgh: Churchill Livingstone 1992: 638–40.
- WOHL ME, CHERNICK V. State of the art: Bronchiolitis. *Am Rev Respir Dis* 1978; 118: 759–81.
- GOODMAN BT, CHAMBERS TL. Bronchodilators for bronchiolitis? *Lancet* 1993; 341: 1380.
- GREEN M, BRAYER AF, SCHENKMAN KA, WALD ER. Duration of hospitalization in previously well infants with respiratory syncytial virus infection. *Pediatr Infect Dis J* 1989; 8: 601–5.
- HENRY RL, MILNER AD, STOKES GM. Ineffectiveness of ipratropium bromide in acute bronchiolitis. *Arch Dis Child* 1983; 58: 925–6.
- PRENDIVILLE A, ROSE A, MAXWELL DL, SILVERMAN M. Hypoxaemia in wheezy infants after bronchodilator treatment. *Arch Dis Child* 1987; 62: 997–1000.
- LENNEY W, MILNER AD. At what age do bronchodilator drugs work? *Arch Dis Child* 1978; 53: 532–5.
- RUTTER N, MILNER AD, HILLER EJ. Effects of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. *Arch Dis Child* 1975; 50: 719–22.
- PHELAN PD, WILLIAMS HE. Sympathomimetic drugs in acute viral bronchiolitis. Their effect on pulmonary resistance. *Pediatrics* 1969; 44: 493–7.
- KLASSEN TP, ROWE PC, SUTCLIFFE T, ROPP LJ, McDOWELL IW, LI MM. Randomised trial of salbutamol in acute bronchiolitis. *J Pediatr* 1991; 118: 807–11.
- MALLOL J, BARRUETO L, GIRARDI G, et al. Use of nebulised bronchodilators in infants under 1 year of age: analysis of four forms of therapy. *Pediatr Pulmonol* 1987; 3: 298–303.
- SCHWEICH PJ, HURT TL, WALKLEY EI, MULLEN N, ARCHIBALD LF. The use of nebulised albuterol in wheezing infants. *Pediatr Emerg Care* 1992; 8: 184–8.
- HO L, COLLIS G, LANDAU LI, LE SOUEF PN. Effect of salbutamol on oxygen saturation in bronchiolitis. *Arch Dis Child* 1991; 66: 1061–4.
- GADOMSKI AM, LICHENSTEIN R, HORTON L, KING J, KEANE V, PERMUTT T. Efficacy of albuterol in the management of bronchiolitis. *Pediatrics* 1994; 93: 907–12.
- KELLNER JD, OHLSSON A, GADOMSKI AM, WANG EE. Efficacy of bronchodilator therapy in bronchiolitis: a meta analysis. *Arch Pediatr Adolesc Med* 1996; 150: 1166–72.
- FLORES G, HORWITZ RI. Efficacy of beta 2 agonists in bronchiolitis. A reappraisal and meta-analysis. *Pediatrics* 1997; 100: 233–9.
- LENNEY W, MILNER AD. Alpha and beta-adrenergic stimulants in bronchiolitis and wheezy bronchitis in children under 18 months of age. *Arch Dis Child* 1978; 53: 707–9.
- CADE A, BROWNLEE KG, CONWAY SP, et al. Randomised placebo controlled trial of nebulised corticosteroid in acute respiratory syncytial viral bronchiolitis. *Arch Dis Child* 2000; 82: 126–30.
- ROOSEVELT G, SHEEHAN K, GRUPP-PHELAN J, TANZ RR, LISTERNICK R. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet* 1996; 348: 292–5.
- WANDSTRAT TL. Respiratory syncytial virus immune globulin intravenous. *Ann Pharmacother* 1997; 31: 648–9.
- VAN WOENSEL JB, WOLFS TF, VAN AALDEREN WM, BRAND PL, KIMPEN JL. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax* 1997; 52: 634–7.
- COUPE MO, GULY U, BROWN E, BARNES PJ. Nebulised adrenaline in acute severe asthma comparison with salbutamol. *Eur J Respir Dis* 1987; 71: 227–32.

23. SANCHEZ I, DE KOSTER J, POWELL RE, WOLSTEIN R, CHERNICK V. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. *J Pediatr* 1993; 122: 145–51.
24. KLASSEN TP. Recent advances in the treatment of bronchiolitis and laryngitis. *Pediatr Clin North Am* 1997; 44: 249–61.
25. WENNERGREN G, KRISTJANSSON S, STEN G, BJURE J, ENGSTROM I. Nebulised racemic adrenaline for wheezy bronchitis. *Acta Paediatr Scand* 1991; 80: 375–7.
26. LOWELL DI, LISTER G, VON KOSS H, MCCARTHY P. Wheezing in infants: The response to epinephrine. *Pediatrics* 1987; 79: 939–45.
27. MENON K, SUTCLIFFE T, KLASSEN TP. A randomised trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995; 126: 1004–7.
28. WAISMAN Y, KLEIN BL, BOENNING DA, et al. Prospective randomised double blind study comparing 1-epinephrine and racemic aerosols in the treatment of laryngotracheitis (croup). *Pediatrics* 1992; 89: 302–6.
29. BUTTE MJ, NGUYEN BX, HUTCHISON TJ, WIGGINS JW, ZIEGLER JW. Paediatric myocardial infarction after racemic epinephrine administration. *Pediatrics* 1999; 104: e9.