Efficacy of Bronchodilator Therapy in Bronchiolitis: A Meta-analysis
[Article]
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Outline

Graphics

Abstracttoctoc
Objective: To determine if bronchodilators are efficacious in treating bronchiolitis.

Data Sources: A search of bibliographic databases (MEDLINE, Excerpta Medica, and Reference Update) for bronchiolitis and albuterol or ipratropium bromide, or adrenergic agents or bronchodilator agents. Reference lists were also used.

Study Selection: Randomized, placebo-controlled trials of bronchodilator treatment in bronchiolitis were selected by 2 investigators. Fifteen of 89 identified publications met the selection criteria.

Data Extraction: Investigators independently abstracted data for 3 outcomes: clinical score, oxygen saturation, and hospitalization. Clinical score was measured as a dichotomous variable (score+/-improved) or continuous variable (average score).

Data Synthesis: For primary analysis, data were pooled from 8 trials of children with first-time wheezing. The effect size for average score was -0.32 (95% confidence interval [CI], -0.54 to -0.11; P<.01), favoring treatment; the relative risk for score+/-improved was 0.76 (95% CI, 0.60 to 0.95; P=.02), favoring treatment. Bronchodilators had no effect on hospitalization (relative risk, 0.85; 95% CI, 0.47 to 1.53; P=.58), but co-interventions may have been administered prior to this outcome. The results for oxygen saturation were too varied to allow pooling of the results. Secondary analyses were performed on 4 outpatient trials of children with first-time wheezing, 7 trials in which only nebulized beta-agonists were used, and on all 15 trials identified. The results were similar, but the data varied more.

Conclusion: Bronchodilators produce modest short-term improvement in clinical features of mild or moderately severe bronchiolitis.

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Bronchiolitis is an acute, highly communicable lower respiratory tract infection, characterized by "cough, coryza, fever, expiratory wheezing, grunting, tachypnea, retractions and air trapping." [1] Its morbidity is high, accounting in 1995 for 17% of all infant hospitalizations (9 admissions per 1000 child-years) in New York State. [2] Infants with bronchiolitis are wheezing for the first time, unlike those with asthma in whom wheezing is recurrent.

Bronchodilators are commonly used in the treatment of bronchiolitis. A Canadian study [3] found that 78% of those who were hospitalized with bronchiolitis received bronchodilators. In a survey of pediatric allergists and pulmonologists in the United States, [4] 86% of the respondents recommended a trial of bronchodilators for this condition. However, bronchodilator efficacy for this illness is not universally accepted, and bronchodilators are seldom used to treat bronchiolitis in the United Kingdom. [5] Randomized clinical trials of bronchodilators in bronchiolitis,

whether for ambulatory or hospitalized children, have yielded variable results. In studies comparing bronchodilators with placebo, some authors have found that bronchodilators are beneficial, [6-13] while others have shown either no benefit [14-19] or a poorer outcome. [20]

Because of the widespread use of bronchodilators despite conflicting evidence regarding their efficacy, we undertook a systematic overview of all randomized placebo-controlled trials of bronchodilators for the treatment of bronchiolitis. This overview reviews the quality of the studies and provides a quantitative summary of the effects of bronchodilators. The question addressed by the meta-analysis was: Are bronchodilators beneficial in the treatment of bronchiolitis as measured by improvement in clinical scores, oxygen saturation, or hospital admission rate?

MATERIALS AND METHODS

STUDY IDENTIFICATION, SELECTION, AND ASSESSMENT OF QUALITY

Three computerized bibliographic databases were searched to find all publications (in all languages) examining bronchodilator therapy of bronchiolitis: the National Library of Medicine MEDLINE database from January 1966 through September 1994; the Excerpta Medica database from January 1974 through November 1995; and Reference Update (Research Information Systems, Carlsbad, Calif) on November 8, 1993; June 29, 1994; and April 26, 1995. The search terms explode bronchiolitis and albuterol or ipratropium or adrenergic agents or bronchodilator agents were used. In addition, the files of 2 of us (J.D.K. and E.E.L.W.) and the bibliographies of all selected articles were examined.

The articles were initially reviewed independently by 2 of us (J.D.K. and E.E.L.W.). Methods and results were examined if the title, text, or both indicated that patients with bronchiolitis were studied in a prospective, randomized clinical trial that compared a bronchodilator with placebo. All articles used the term bronchiolitis to refer to an acute lower respiratory tract infection with wheezing. Only studies that were published as complete manuscripts and that assessed symptoms or signs were included. Thus, studies that assessed pulmonary function alone were excluded. Both reviewers (J.D.K. and E.E.L.W.) were completely concordant in the selection of the articles for review. Data were abstracted independently by each investigator. Unpublished data were requested from authors when necessary. The quality of each study was evaluated by assessing whether double blinding and concealment of allocation to treatment groups were adequately reported, based on the criteria of Schulz and colleagues. [21]

SELECTION OF OUTCOME MEASURES

Clinical scores, based on a multi-item scale, oxygen saturation (oximetry), and admission to hospital (admission), were selected to measure the effect of bronchodilators. These were thought to be the most clinically relevant measures and to have the largest amount of experimental data reported. Respiratory rate was not selected as an isolated measure because of many uncontrollable factors that influence respiratory rate. [15]

Clinical scores were reported in 2 ways: (1) as the proportion of subjects with an improved score based on an a priori determination of significant clinical improvement (score+/-improved, a

dichotomous variable), [6,8,9,11,12,16-18] and (2) as the average score or change in score in each treatment group (average score, a continuous variable). [8-10,13-15,19]

META-ANALYSIS

For the 2 continuous variables (average score and oximetry), the effect of treatment compared with placebo was determined by the unbiased estimate of effect size (ES), with its 95% confidence interval. [22] For average score, an ES of less than 0 (ie, reduction of severity scores) indicates a benefit, and an ES of more than 0 (ie, increased severity scores) indicates that treatment is detrimental. Alternatively, for oximetry, an ES of less than 0 (ie, reduced oxygen saturation) indicates a detrimental effect, and an ES of more than 0 (ie, increased oxygen saturation) indicates a benefit.

For the 2 dichotomous variables (score+/-improved and admission), the effect of treatment compared with placebo was determined by the Mantel-Haenszel relative risk (RR), with 95% confidence interval. [22] For score+/-improved, the RR is the ratio of proportions not improved in the treatment and placebo groups. An overall RR of less than 1 (ie, fewer subjects not improved in the treatment group compared with the placebo group) indicates that treatment is beneficial, while an RR of more than 1 indicates that treatment is detrimental.

A fixed-effects model was used in the meta-analysis. [23] This model assumes that the true effect of treatment is similar in all trials and that any difference in treatment effect between trials is due to chance. Because individual studies include different patients and use slightly different treatment regimens and outcome measures, the pooled data will appear heterogeneous. [24] Large differences in direction or magnitude of effects between studies will demonstrate statistical heterogeneity and the pooled estimate of effect may be invalid. [24] Although pooling data increase the power to measure an overall treatment effect, the power to detect heterogeneity between trials will be limited if the sample size of individual trials is small. [25] For this reason, it has been suggested that a higher than usual P value of.10 or less be used to indicate significant heterogeneity. [26]

All statistical analyses were performed on a personal computer, using the following software packages: SAS (SAS Institute Inc, Cary, NC), Revman (Cochrane Collaboration, Oxford, England), and Minitab (Philadelphia, Pa).

SELECTION OF TRIALS FOR PRIMARY AND SECONDARY ANALYSES

The primary analysis included only trials that reported data on patients who were wheezing for the first time. To evaluate the influence of differences in patient population and study methods, the following groups of trials were considered in secondary analyses: (1) all subjects or trials regardless of whether subjects had previous wheezing, (2) trials that used nebulized beta-adrenergic agents only, and (3) outpatient trials of subjects wth first-time wheezing. Data were pooled for these analyses if 2 or more trials were included in each group. Other secondary analyses were considered that included grouping by age (<or= to 12 months) and dose of bronchodilator. However, no sufficient data existed for these measures to allow appropriate grouping.

RESULTS toctoc

STUDY SELECTION toctoc

Fifteen of 89 identified articles were included in the analysis. [6-12,14-20] Excluded from the study were 66 articles that were not clinical trials; 3 randomized controlled trials that did not have a placebo group (albuterol was compared with racemic epinephrine, [27] ipratropium bromide [28] and corticosteroids [29]); 1 article that was a cohort study of theophylline [30]; 1 study that was published as an abstract only [31]; 1 Russian study that had an inadequate description of the patients and methods [32]; and 2 studies that used evaluations of pulmonary function studies as the only outcome. [33,34] A log of rejected articles is available from us on request.

In 8 included trials, [7,8,12,14,15,18-20] results were reported from subjects who were wheezing for the first time. The remaining 7 trials, [6,9-11,13,16,17] in which data about subjects with first-time wheezing could not be separated from those about subjects with recurrent wheezing, were included only in the secondary analysis. On request, 6 authors provided additional data not stated in their publications. [7-10,12,15,20]

CHARACTERISTICS OF INDIVIDUAL TRIALS toctoc

The design and quality features of each study are shown in (Table 1). Excluded from the final data set were 139 patients representing a portion of the patients from several trials; of these, 53 patients were not randomized, [6,14] 37 were older than 12 months and had recurrent wheezing, [10] and 49 patients had also received corticosteroids. [11,17] A total of 734 patients were included (419 outpatients and 315 inpatients). Data from 2 studies on subjects treated with nebulized or oral albuterol [14,15] were analyzed separately. In all but 2 studies, subjects had mild or moderately severe illness (Table 1). In these remaining studies, disease severity was not explicitly stated; however, the data seem to indicate that subjects with severe disease were excluded. [13,16]

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Table 1. Features of Trials Included in Meta-analysis*

Laboratory methods to identify respiratory syncytial virus (RSV) included direct immunofluorescence microscopy, [7,8,10,14,18-20] culture, [6,15,19] enzyme immunoassay, [9] and serum RSV titers. [6,17] The range of subjects who were RSV positive was 3% to 100%, with more than 40% RSV-positive subjects in 8 trials. [7,8,10,14,15,18-20]

The dose of nebulized albuterol was 0.15 mg/kg in 6 studies [7,10,14,15,17,19] and 0.1 mg/kg in 1 study. [8] In other studies, the dose of nebulized albuterol was 2 mg [18] or 2.5 mg. [20] The dose of oral albuterol was 0.15 mg/kg in 2 studies [14,15] and 2.5 mg in 1 study. [17] Other beta-agonists were epinephrine bitartrate (0.01 mg/kg subcutaneously), racemic epinephrine (2-5 mg,

depending on weight, nebulized), [6,13] fenoterol (0.2 mg/kg, nebulized or oral, [11] and metaproterenol sulfate (10 mg, nebulized). [9] The dose of nebulized ipratropium bromide was 0.25 mg in 4 studies, [11,12,16,19] and, in 1 study, the dose for infants younger than 6 months was 0.125 mg. [19]

Adverse effects noted to be significantly or exclusively found in the study groups receiving bronchodilator(s), compared with placebo, included tachycardia (P<.05), [8,18] increased blood pressure level (P<.01), [13] decreased oxygen saturation (P<.05), [10,20] flushing (1 patient [9] and 4 patients [15]), hyperactivity (3 patients), [15] tachycardia and prolonged cough (2 patients), [16] and tremor (1 patient each). [17,19]

CLINICAL SCALEStoctoc

Several multi-item clinical scales or scores were used. All start at 0 (indicating no distress) and increase to an upper limit (indicating severe distress). The Respiratory Assessment Change Score consists of changes in the Respiratory Distress Assessment Instrument, measuring wheezing and retractions, and changes in respiratory rate. [6] The Respiratory Assessment Change Score was used in 3 studies, [6,12,18] and the Respiratory Distress Assessment Instrument component was used in 2 studies. [8,10] Two scales were modifications of a previously reported scale for children with wheezing [35] : one modified by Tal et al [17] who used a 4-item scale, ie, respiratory rate, wheezing, cyanosis, and accessory muscle use (this scale was used in 2 studies [11,17]); the other modified by Wang et al [19] who differentiated a 4-item scale as follows: respiratory rate, wheezing, accessory muscle, use and general condition. Gadomski et al [14,15] developed a 9-item scale (used in their 2 studies [14,15]), which included grunting, nasal flaring, supraclavicular retractions, intercostal retractions, air entry, air hunger, duration of wheeze, location of wheeze, and general appearance. Alario et al [9] developed the 6-item Respiratory Distress Index: color, wheezing, accessory muscle use, flaring, grunting, and distress (used in 1 study of theirs [9]). Kristjansson et al [13] developed a 5-item scale: respiratory rate, intercostal recessions, auscultatory breath sounds, skin color, and general condition. Henry et al [16] used heart rate, respiratory rate, and 11 items reflecting respiratory distress. Finally, Schuh et al [7] used accessory muscle score and wheeze score, in addition to heart rate and respiratory rate, each item having been considered separately. None of these latter 4 items was used in the meta-analysis, because no single item was shown to be more valid or reliable as a measure of clinical change.

ANALYSIS OF POOLED DATAtoctoc

(Table 2) gives the values for each variable in the treatment and placebo groups in each study. The sample sizes and time of assessments after therapy are also given. (Table 3) gives the results of the meta-analyses for each variable for the primary and secondary analyses.

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Table 2. Outcomes Used for Meta-analysis

Table 3. Pooled Outcomes for Effect of Bronchodilators in Bronchiolitis*

Primary Analysistoctoc

The dichotomous variable (score+/-improved) and continuous variable (average score) each showed a significant effect, favoring treatment. Overall, 54% of subjects in the treatment groups improved compared with 25% of subjects in the control groups (P<.001). For average score, the condition of treated patients was more likely to improve.

The individual trial results for this variable are shown graphically in (Figure 1). No significant effect of treatment on hospital admission rate was noted; it was less than 25% in all but 2 of the study groups for all of the analyses.

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Figure 1. Improvement in clinical score with nebulized (neb) and oral (po) bronchodilators for the treatment of bronchiolitis. Effect size and 95% confidence intervals (bars). See the "Clinical Scales" subsection in the "Results" section text and (Table 2) for additional details.

No significant effect of treatment on oximetry was noted; however, the data were heterogeneous. The heterogeneity in this primary analysis resulted from a difference in direction of treatment effect between studies. In 4 studies, the oxygen saturation was higher in the treatment group, whereas in 2 studies it was lower and in 3 studies it was not different in treatment vs placebo group. None of the study groups in the primary analysis and only 3 groups in the secondary analysis of all studies had an average score of less than 93%. Also, the difference in average score between treatment and placebo groups was 2.2% or less in all but 1 trial.

Secondary Analysistoctoc

The secondary analysis produced results that were similar to the primary analysis; however, some results were more heterogeneous. For score+/- improved, the data were more heterogeneous than with the primary analysis, both for all subjects regardless of previous wheezing and for subjects who received inhaled beta-adrenergics only. The heterogeneity in these analyses resulted from a difference in the magnitude, rather than direction, of proportions improved in each study. In all studies, the condition of more patients improved in the treatment

groups than in the placebo groups; however, in several studies, the proportion of improved subjects in the treatment group was much greater than in the placebo group (Table 2). [6,9,11]

COMMENTtoctoc

This meta-analysis of young children with mild and moderately severe bronchiolitis has shown that bronchodilators produce a short-term improvement in clinical scores. Heterogeneity of data between studies prevents a conclusion about whether bronchodilators benefit oxygen saturation. The reported data do not show any benefit to prevent hospitalization in this population without severe disease.

Whether the improvement in clinical score is large enough to routinely initiate bronchodilator therapy deserves further study. There is a subgroup of children in whom bronchiolitis will respond to bronchodilator therapy. In an individual child with bronchiolitis, a trial of therapy with bronchodilators is warranted. However, a valid assessment indicating improvement should be made before continuing treatment. Gadomski et al [14] have suggested that improvement in clinical scores may result from changes in physiological state (eg, change from asleep to awake) rather than from improved respiratory function with bronchodilator therapy.

There was heterogeneity in the secondary analysis of clinical score as a dichotomous variable (score+/-improved). A likely explanation for this heterogeneity is that the pooling of trials included children with recurrent wheezing, in whom response to bronchodilator therapy is more likely than in those with first-time wheezing. Other possible explanations for the heterogeneity are differences in what the clinical scores are measuring, variation in timing of the clinical evaluation, and confounding with state variation, as previously discussed.

The heterogeneity of data on oxygen saturation with all analyses precludes any conclusion about the value of oximetry as a measure. However, explanations for heterogeneity can be considered. The most likely explanation is that the trials included only subjects with mild or moderately severe disease. The difference in oxygen saturation between treatment and placebo groups was small in all studies, and the absolute value for average oxygen saturation was high. Thus, the effect of bronchiolitis on oxygen saturation may be limited and inconsistent with less severe disease.

The lack of benefit from bronchodilators to prevent hospitalization is of uncertain significance. In all outpatient studies, the decision to admit was made after the study was completed. This decision was made by nonstudy physicians, and further treatment may have been given, regardless of the intervention received during the study. Thus, this outcome was unlikely to reflect only the initial intervention provided in the study.

The cost of bronchodilator therapy for bronchiolitis is not insignificant. A conservative estimate of the total cost can be made. In the United States, the number of children in each of the first 2 years of life is approximately 4.2 million, after subtracting infant mortality. [2] In this age group, annually about 75 000 children are admitted to hospitals because of bronchiolitis. [2] Only 5% to 10% of children with bronchiolitis require hospitalization. [36] Thus, there will be at least 675 000 ambulatory children each year. For this example, considering that 80% of the children are

treated, [3,4] the cost of treatment can be estimated at $50 per child (metered-dose inhaler and spacer for outpatients or nebulized bronchodilator, tubing, and mask for inpatients). Thus, the estimated total annual cost to provide bronchodilator therapy to children with primary RSV-positive bronchiolitis would be $37.5 million.

The widespread use of bronchodilators in the management of bronchiolitis is likely caused by the similarity of symptoms and signs of bronchiolitis and asthma. Bronchodilators are effective in the treatment of asthma, in which airway obstruction is caused by inflammation, bronchospasm, and bronchial hyperreactivity. [37] The pathophysiologic features of bronchiolitis include terminal bronchiolar and alveolar inflammation with airway swelling and luminal debris, which lead to airway obstruction. [38] In addition, mediators of bronchospasm have been shown to be present in variable amounts in children with bronchiolitis. [38] Not all children with bronchiolitis likely have the same propensity to have bronchospasm and bronchial hyperreactivity.

Bronchodilators produce modest short-term improvement in clinical features of mild or moderately severe bronchiolitis. Data about the efficacy of bronchodilators in the management of bronchiolitis beyond the emergency department visit are inadequate. Because of the large number of infants afflicted with bronchiolitis, further placebo-controlled trials of bronchodilators are needed. Future studies should carefully distinguish subjects with first-time wheezing from those with recurrent wheezing, consider severely ill children, and evaluate the outcome of therapy throughout the course of illness.

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Albuterol; Bronchodilator Agents; Bronchiolitis; Hospitalization; Ipratropium; Meta-analysis; Respiratory Sounds; Wheezing