Efficacy of oral dexamethasone in outpatients with acute bronchiolitis

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Objective: To examine the efficacy of oral dexamethasone in acute bronchiolitis.

Study design: A double-blind randomized, placebo-controlled trial involving 70 children <24 months old in the emergency department with Respiratory Disease Assessment Instrument ≥6. Each patient received either 1 dose of 1 mg/kg of oral dexamethasone or placebo and was assessed hourly for a 4-hour period. Repeated measures regression analysis evaluated a change in the Respiratory Assessment Change Score (RACS).

Results: The 2 groups had similar baseline characteristics with Respiratory Disease Assessment Inventory of 9.4 ± 2.3 in the dexamethasone group (n = 36) and 10.0 ± 2.7 in the placebo group (n = 34). The RACS was −5.0 ± 3.1 in the dexamethasone group and −3.2 ± 3.7 in the placebo group (P = .029).

Poor RACS occurred in 41% and 17% of the placebo and dexamethasone groups, respectively (P = .054). Of the children treated with dexamethasone, 19% were hospitalized compared with 44% in the placebo group (P = .039).

There was no difference in RACS between the groups on day 7 (P = .75).

Conclusion: Outpatients with moderate-to-severe acute bronchiolitis derive significant clinical and hospitalization benefit from oral dexamethasone treatment in the initial 4 hours of therapy. (J Pediatr 2002;140:27–32.)

Acute bronchiolitis is the most frequent cause of infant hospitalizations during yearly winter outbreaks. Approximately 60% of children with bronchiolitis respond modestly to inhaled bronchodilators; however, a significant impact on hospitalizations has not been demonstrated. Although airway inflammation is one of the pathologic hallmarks of bronchiolitis, the efficacy of corticosteroids is not established. This lack of evidence is contrary to expectations of benefit because of the pathophysologic features of bronchiolitis and the proved efficacy of corticosteroids in the closely related childhood respiratory diseases asthma and croup. Partial explanation for this disparity relates to methodologic issues around previous trials of this therapy. Previous studies have been carried out with...
METHODS

Study Patients

One trained study nurse was notified of all children with acute bronchiolitis who were seen between 8 AM and 9 PM in the emergency department of this hospital between November 1997 and April 2000. Children were enrolled if they were between 8 weeks and 23 months old, had the first wheezing episode associated with respiratory distress and an upper respiratory tract infection, and received a Respiratory Disease Assessment Instrument (RDAI) rating13 of ≥6 at baseline. Exclusion criteria included children with previous history of wheezing or bronchodilator therapy, prematurity, neonatal ventilation, chronic lung/cardiac disease, aspiration, neurologic/neuromuscular problems, and immunodeficiency. We also excluded critically ill infants who required immediate airway stabilization, infants previously given oral or inhaled corticosteroids, and infants exposed to varicella within 21 days before arrival. The study was approved by the Human Ethics Review Board of this institution, and written consent was obtained from each patient’s parents before enrollment. A log of patients who were missed, excluded, or refused to participate was kept to assess the generalizability.

Study Design

Eligible children were assigned randomly to 1 of 2 groups that both received the same dosage (1 mg/kg) of treatment; the dexamethasone group received a single dose of oral dexamethasone syrup (Merck Frosst, Canada & Co, Pointe-Claire, Dorval, Québec, Canada), and the placebo group received a single dose of placebo syrup with double blinding.9 They also received nebulized albuterol (Ventolin 5% solution, GlaxoWellcome, Inc, Mississauga, Ontario, Canada) via a vented Pari LC STAR (Pari Respiratory Equipment, Midlothian, Va) nebulizer 2.5 mg per dose (0.5 mL) in 5 mL of normal saline solution, with oxygen flow of 6 to 7 L/min with a tight-fitting face mask at times 0, 30, 60, and 120 minutes. Children discharged home after the 4-hour observation period continued to receive either daily oral dexamethasone (0.6 mg/kg/dose) or placebo for 5 days, on the basis of the previous randomized trial, as well as the albuterol (1.5 mg [0.3 mL]) 4 times daily with the same nebulizer. Clinical outcomes were assessed hourly between baseline and 240 minutes in the emergency department and at the patient’s home on day 7 by the second research nurse. The parents of all patients were telephoned on day 28 to monitor symptom resolution and relapses. The research pharmacist assessed compliance with the experimental therapy by measuring the volume of the experimental syrup and the albuterol solution before and after the study.

Delivery of the Experimental Therapy

The experimental dexamethasone syrup was prepared from the intravenous dexamethasone solution flavored with wild cherry syrup; the latter flavoring was also given to the group taking the placebo. The active therapy and placebo were of identical color, texture, taste, and smell. The identity of the treatment assignment was completely masked to patients, family, clinicians, and research personnel with the exception of the research pharmacists. The dose was repeated once in cases of vomiting within 20 minutes of administration, and further vomiting necessitated withdrawal from the study.

Randomization

A blocked randomization code was prepared by our pharmacy from a computer generated list of random numbers. The pharmacy prepared sequential sealed packets containing the experimental drugs. The randomization code was revealed only after all patients had completed the study.

Other Treatments and Dispositions

Nasopharyngeal swabs for virology were done before discharge. Children who had persistent signs of respiratory distress 240 minutes after experimental therapy were admitted to the hospital. All decisions regarding the need for further treatment and hospitalization were made by the attending physicians not involved in this study who were unaware of the research nurse’s scoring as well as the patients’ treatment assignment. The attending physicians were requested not to administer additional therapy (other than acetaminophen for fever) unless the patient’s condition deteriorated significantly. Hospitalized patients were given nebulized albuterol only and supportive treatment as indicated. To encourage compliance with the experimental therapy after discharge, all patients were issued a letter for their primary care provider. Additional treatments during this period were recorded during the home visit on day 7.

Outcome Measures

The Respiratory Assessment Change Score (RACS)14 measured from time 0 to 240 minutes after experimental intervention, recorded by 1 previously trained research nurse, was the primary outcome measure. RACS assesses changes in the retractions and wheezing as measured by changes in the Respiratory Disease Assessment Instrument (RDAI)13 and change in respiratory rate.14 The RDAI assigns a maximum of 8 points for wheezing and 9 points for retractions, depending on the location and severity of these 2 signs.13 The changes in RDAI from one point to another were assessed by subtracting the scores of the latter reading from those of the earlier one. Interval changes in respiratory rate were standardized according to the child’s baseline. A change of ≤5% in the respiratory rate from baseline was
counted as a change of 0 units, a decrease/increase of 6% to 15% as an improvement/deterioration of 1 unit, etc. The overall RACS was calculated as the arithmetic sum of the RDAI change and of the standardized respiratory rate change. For example, a patient whose RDAI improved from 10 to 5 units (decrease of 5 units) and whose respiratory rate changed from 60 to 48 breaths per minute (decrease of 20%; ie, 2 units) had RACS of \((-5) + (-2)\). A decrease in RACS represents improvement, whereas an increase signifies deterioration. Internal validity and responsiveness of the RACS, as a measure of acute respiratory compromise in noncritically ill infants has been demonstrated.10,13,14 The RACS correlates well with other clinical measures of respiratory distress including inspiratory/expiratory ratio, grunting, nasal flaring, and social interactiveness.14 Secondary outcomes included differences in hospitalization rates after the 240-minute observational period, changes in transcutaneous oxygen saturation, and the measurement of the RACS from baseline to day 7. Poor response to therapy was defined as RACS of \(-2\) or less (ie, \(-2, -1, \) etc) at 240 minutes. Before the study, both research nurses were trained in the measurement of the clinical score on a population of children with bronchiolitis with a wide range of disease severity. An intraclass correlation coefficient of 0.91 was obtained with respect to interrater reliability testing of the RACS on a sample of 20 children with this disease.

**Analysis**

The sample size was calculated on the basis of the estimated SD in the RACS from baseline to 240 minutes in the control group (n = 5). The study was designed to detect a difference in the mean change score between the groups of 2. With an \(\alpha\) of .05 and \(\beta\) of .20, the sample size required to detect this difference was estimated to be 71 children. Differences in mean values between the dexamethasone and placebo groups were tested with the Student t test, and proportions were compared with the Fisher exact test. The change in clinical scores over 4 hours was evaluated by repeated measures regression analysis, with treatment group, age, history of eczema, family history of atopy, baseline RDAI, family history of smoking, and albuterol treatment before randomization as independent variables. Logistic regression analysis was used to assess the effects of these covariates on the risk of hospitalization.

**RESULTS**

**Characteristics of the Patients**

During the three 6-month winter periods between November 1997 and April 2000, 1464 children arrived in our emergency department with a first-time episode of wheezing that was diagnosed as bronchiolitis. Of these 1464 children, 920 were not approached because the research nurse was not present. The children who arrived during the recruitment periods but had to be excluded from the study were (1) 91 younger than 8 weeks, (2) 140 with baseline RDAI <6, (3) 43 who were taking corticosteroids, (4) 37 who had unstable conditions and were hospitalized shortly after their arrival, (5) 51 who had concurrent cardiopulmonary disease or history of ventilation, (6) 2 who had been in contact with varicella, and (7) 63 for other reasons (eg, language difficulty). Forty-six families declined to participate; thus, 71 children were recruited and selected for the experimental therapy. One parent changed his mind before therapy was started, leaving 70 patients for analysis (36 in the dexamethasone group and 34 in the placebo group).

### Table I. Baseline characteristics of the 2 groups

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone group (n = 36)</th>
<th>Placebo group (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>20/16</td>
<td>23/11</td>
</tr>
<tr>
<td>Age (m)*</td>
<td>6.1 ± 3.5</td>
<td>6.9 ± 3.9</td>
</tr>
<tr>
<td>Eczema history</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Duration of respiratory distress (h)</td>
<td>40.5 ± 33.1</td>
<td>42.8 ± 35.5</td>
</tr>
<tr>
<td>Medications before arrival</td>
<td>Inhaled albuterol</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Oral albuterol</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Orciprenaline</td>
<td>2</td>
</tr>
<tr>
<td>Clinical status</td>
<td>RDAI*</td>
<td>9.4 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>RDAI range</td>
<td>6-16</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate* (/m)</td>
<td>52.3 ± 10.7</td>
</tr>
<tr>
<td></td>
<td>Oxygen saturation* (%)</td>
<td>96.8 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>Heart rate* (/m)</td>
<td>142.6 ± 17.7</td>
</tr>
<tr>
<td></td>
<td>Temperature &gt;38°C</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>RSV positive†</td>
<td>15/28</td>
</tr>
</tbody>
</table>

RSV, Respiratory syncytial virus.

*Mean ± SD.

†Parents have refused nasopharyngeal swab in 8 patients in the dexamethasone group and 4 patients in the placebo group.
from the emergency department, 39 of whom had parents who agreed to continue the experimental therapy at home (dexamethasone group = 26, placebo group = 13). Two families refused a house visit, and one child lived outside commuting distance; therefore, 67 of the 70 participating children were re-evaluated at home on day 7 (dexamethasone group = 35, placebo group = 32). We were able to contact 65 families by telephone on day 28 (dexamethasone group = 36, placebo group = 29).

**Clinical Outcomes in the Emergency Department**

The RACS from baseline (time 0) to 240 minutes demonstrated a significantly greater overall improvement in respiratory distress in the dexamethasone group compared with the placebo group (Table II, Figure). Repeated measures regression showed that the treatment group only was associated with a significant difference in response, whereas the age, history of atopy, baseline RDAI, or treatment with racemic epinephrine were not. The difference in improvement in wheezing and retractions as measured by the RDAI between the 2 groups approached statistical significance (Table II). The trends in changes in respiratory rate were also consistent with greater improvement in the dexamethasone group. However, this trend did not achieve statistical significance (Table II). In the dexamethasone group, 6 of 36 infants (17%) exhibited poor response, whereas 14 of 34 infants (41%) taking the placebo responded poorly ($P = .034$). Furthermore, 17 of 36 children (47%) in the dexamethasone group had achieved a mild disease severity (defined as RDAI ≤5) at 240 minutes compared with 8 of 34 children (24%) treated with the placebo ($P = .054$). Interestingly, 17 of 36 children (47%) in the dexamethasone group had an admission for persistent respiratory distress, whereas 14 of 34 infants (41%) taking the placebo responded poorly ($P = .034$). Furthermore, 17 of 36 children (47%) in the dexamethasone group had achieved a mild disease severity (defined as RDAI ≤5) at 240 minutes compared with 8 of 34 children (24%) treated with the placebo ($P = .054$). Five children received racemic epinephrine during the study because of persistent respiratory distress, one in the dexamethasone group and four in the placebo group. Therapy with epinephrine was not significantly associated with treatment effect.

**Hospitalization**

The rate of hospitalization from the emergency department was significantly higher in the placebo group (22/34 infants, 65%) than in the dexamethasone group (9/31 infants, 29%) ($P = .034$). Nine children (25%) in the dexamethasone group required medical attention for continuing symptoms between day 7 and day 28, and 14 infants (48%) in the placebo group required medical attention associated with hospitalization. Of the 22 hospitalized children, 21 were admitted after the 240 minutes of the initial treatment and outcome assessment, and one required hospitalization shortly after the initial discharge. None of the other children who were initially sent home were subsequently hospitalized.

**Clinical Outcome on Days 7 and 28**

The intent-to-treat analysis showed no significant clinical or statistical difference in the RACS between the 2 experimental groups on day 7 (Table II). Of the 67 infants re-evaluated on day 7, 36 infants were sent home (dexamethasone group = 25, placebo group = 12). We were able to contact 65 families by telephone on day 28 (dexamethasone group = 36, placebo group = 29).

### Table II. Clinical parameters in the 2 groups at 4 hours and 7 days

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone group</th>
<th>Placebo group</th>
<th>P value*</th>
<th>Dexamethasone group</th>
<th>Placebo group</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 36)</td>
<td>(n = 34)</td>
<td></td>
<td>(n = 35)</td>
<td>(n = 32)</td>
<td></td>
</tr>
<tr>
<td>RACS‡ at 4 h</td>
<td>Mean –5.0 ± 3.1</td>
<td>–3.2 ± 3.7</td>
<td>.029</td>
<td>–8.9 ± 5.2</td>
<td>–9.3 ± 4.9</td>
<td>.750</td>
</tr>
<tr>
<td>Median</td>
<td>–5</td>
<td>–3</td>
<td></td>
<td>–9</td>
<td>–10</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>–13 to +4</td>
<td>–9 to +8</td>
<td></td>
<td>–18 to +8</td>
<td>–20 to 0</td>
<td></td>
</tr>
<tr>
<td>RDAI‡ at 7 d</td>
<td>Mean 5.4 ± 2.1</td>
<td>7.2 ± 2.8</td>
<td>.064</td>
<td>2.4 ± 3.1</td>
<td>2.6 ± 3.0</td>
<td>.754</td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
<td>7</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-10</td>
<td>2-14</td>
<td></td>
<td>0-12</td>
<td>0-11</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (l/m)‡</td>
<td>45.8 ± 7.8</td>
<td>50.1 ± 10.8</td>
<td>.125</td>
<td>42.0 ± 8.4</td>
<td>42.7 ± 7.7</td>
<td>.982</td>
</tr>
<tr>
<td>Oxygen saturation (%)‡</td>
<td>96.4 ± 2.8</td>
<td>95.7 ± 5.0</td>
<td>.944</td>
<td>164.9 ± 18.4</td>
<td>166.9 ± 16.4</td>
<td>.126</td>
</tr>
<tr>
<td>Heart rate (l/m)‡</td>
<td>164.9 ± 18.4</td>
<td>166.9 ± 16.4</td>
<td>.152</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P value related to the difference in improvement in the parameters from baseline to 4 hours between the groups.
†P value related to the difference in improvement in the parameters from baseline to day 7 between the groups.
‡Mean ± SD.
DISCUSSION

In our trial involving pediatric outpatients with acute bronchiolitis, the overall clinical improvement in the initial 4 hours among those given dexamethasone was greater than among those treated with placebo. The hospitalization rate in the dexamethasone group was less than one half that in the placebo group.

Although a recent meta-analysis suggests significantly greater improvement in the hospitalized infants with bronchiolitis treated with corticosteroids than infants treated with placebo, previous individual studies have not found significant benefit of corticosteroid therapy in this disease. However, they have been performed exclusively in hospitalized infants with a potentially different patient population. Furthermore, the outcomes were not usually measured until 12 to 24 hours after the experimental intervention, and a potential earlier improvement in the treated group could not be ascertained. Several authors have included children with previous wheezing, some of whom may have had asthma and only one study used a previously validated bronchiolitis score. Although the inpatient studies by Tal et al and Goodwin et al had shown significantly faster hospital discharge after treatment with corticosteroids, these studies were limited by inclusion of children with previous wheezing, infrequent assessments, and in the latter, a retrospective design and nonparallel comparison groups. In contrast, our study population consisted of only the first-time wheezers in the early phase of the disease in the outpatient setting. Therefore, the airway obstruction in our patients may have been less established and more easily controlled. These characteristics and exclusion of children with mild disease may have maximized the likelihood of response to corticosteroids. The majority of studies demonstrating benefit of corticosteroids in asthma and croup have also been in outpatients. The 4-hour response interval had been chosen because this is the time frame for disposition decisions. Furthermore, there is accumulating evidence for the benefit of corticosteroids 2 to 4 hours after corticosteroid administration in asthma. The proposed biologic mechanism includes upregulation of β2-receptors, mucosal vasoconstriction, and decrease in airway edema. Because airway inflammation and edema constitute an integral part of the pathophysiologic features of bronchiolitis, this mechanism likely played a role in our study. Recent evidence shows elevated levels of interleukins and other inflammatory mediators in babies with bronchiolitis. Corticosteroids affect synthesis of inflammatory cytokines in asthma and may also do so in bronchiolitis. There is significant in vitro inhibition of RSV-stimulated increases of interleukin 8 and RANTES (regulated on activation, normal T expressed and secreted) after treatment with fluticasone propionate; thus, corticosteroids may inhibit virus-induced chemokine production by airway cells. Because this immunologically mediated mechanism takes many hours to reach full effect, the effect size at 12 to 24 hours may have been even greater.

The choice of the experimental therapy and its dose was influenced by previous bronchiolitis trials. Because previous studies have not demonstrated benefit of corticosteroids, we have used a generous dexamethasone dose to prevent undertreatment of some patients. The optimal dose and duration of corticosteroid therapy in bronchiolitis have yet to be determined. Multiple regression adjusted for family history of atopy confirmed the independent effect of treatment with dexamethasone. Although our study did not find an association between atopy and the outcome, future trials with a stratified randomization on this variable are indicated to further clarify this point.

Many more patients taking placebo than dexamethasone received corticosteroids after discharge, suggesting inferior response to continuing this intervention. Nevertheless, we were unable to show a difference in other outcomes between the 2 groups on day 7. The natural tendency of bronchiolitis to improve with time may have played a role in reducing our power to detect a significant difference. In addition,
cotherapy with steroids, which deferentially involved the placebo group more than the steroid-treated group, could have the effect of reducing the difference between the 2 groups. Therefore, because of the small number of patients who continued the experimental therapy after discharge and the cotherapy after initial treatment, any conclusions about this latter secondary phase must be interpreted with caution.

We conclude that children arriving at the emergency department with moderate-to-severe bronchiolitis derive significant clinical benefit and reduced risk of hospitalization from stabilization with dexamethasone 4 hours after administration. Further trials addressing this issue are indicated to confirm this finding.

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REFERENCES