Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis

Job B M van Woensel, Tom F W Wolfs, Wim M C van Aalderen, Paul L P Brand, Jan L L Kimpen

Abstract
Background — Experimental and clinical evidence suggests that respiratory syncytial virus (RSV) bronchiolitis is an immune mediated disease. Corticosteroids might therefore be effective in the treatment of RSV bronchiolitis.

Methods — A randomised double blind trial was conducted in children up to two years of age admitted to hospital with RSV bronchiolitis to compare prednisolone (1 mg/kg/day orally for seven days) with placebo. Variables used for the efficacy analysis were a daily symptom score and the length of time in hospital in the non-ventilated patients, and the duration of mechanical ventilation and the length of time in hospital in the ventilated patients.

Results — Fifty four patients were included in the trial, 40 of whom were non-ventilated (20 in each group) and 14 were ventilated (seven in each group). During the first three days of treatment the symptom score decreased significantly faster in the prednisolone group than in the placebo group (mean (SE) decrease −1.2 (0.2) points/day versus −0.6 (0.2) points/day; p = 0.02). The mean duration of hospital stay of all 40 non-ventilated patients was not significantly different between the two groups. In the ventilated patients the duration of mechanical ventilation was not significantly different, but the length of time in hospital was six days shorter in the prednisolone group than in the placebo group (mean (SE) 11.0 (0.7) versus 17.0 (2.0) days; p = 0.02 (95% CI) difference = −7.0 (1.8 to 10.2) days; p<0.01).

Conclusions — These results suggest that prednisolone may be effective in accelerating the clinical recovery of children admitted to hospital with RSV bronchiolitis.

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Keywords: respiratory syncytial virus, bronchiolitis, corticosteroids, treatment.

Respiratory syncytial virus (RSV) is the most important cause of viral bronchiolitis in young children. Moreover, RSV is the causative pathogen in most children admitted to hospital with lower respiratory tract infections in the winter. Although the pathogenesis of RSV bronchiolitis is not fully understood, increasing experimental evidence suggests that the host immune response plays an important role. In addition, both pathological and clinical analogy exists between RSV bronchiolitis and childhood asthma. Similar cell types are involved, and RSV bronchiolitis is frequently followed by recurrent episodes of wheezing later in childhood. Based on the immunopathogenesis of RSV bronchiolitis and its analogy with asthma, corticosteroids might theoretically be a therapeutic option. The effect of corticosteroids in children with bronchiolitis has been studied previously, but results of these studies are inconsistent. Most studies were not confined to patients with microbiologically confirmed RSV bronchiolitis. One study demonstrated no effect of corticosteroids in confirmed RSV cases. However, patients at risk for severe disease were excluded. To determine the effect of prednisolone on the clinical course of children admitted to hospital with RSV bronchiolitis, including patients with severe disease, we conducted a prospective randomised double blind placebo controlled trial.

Methods

STUDY POPULATION

All children younger than two years with microbiologically confirmed RSV bronchiolitis admitted to the Beatrix Children’s Hospital between December 1992 and April 1995 were included after written informed consent was obtained from parents or caretakers. Bronchiolitis was defined as acute tachypnoea, wheezing and/or decreased breath sounds, cyanosis and the use of accessory respiratory muscles, in the presence of an apparent viral infection. RSV infection was confirmed by direct immunofluorescence assay using fluorescein isothiocyanate (FITC)-labelled monoclonal antibodies of Imagen (Novo Nordisk Diagnostics Ltd, Cambridge, UK). Patients who had used corticosteroids (systemic or by inhalation) during the two months before admission were excluded. The study was approved by the medical ethics committee of the hospital.

STUDY DESIGN

Patients were randomly allocated to the treatment or placebo groups by the hospital phar-
Table 1 Characteristics of the patients at entry to the study

<table>
<thead>
<tr>
<th></th>
<th>Prednisolone (n=27)</th>
<th>Placebo (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) age</td>
<td>3.3 (1.4–5.9)</td>
<td>3.9 (1.9–6.1)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>9:18</td>
<td>10:9</td>
</tr>
<tr>
<td>Family history of</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>atopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk group</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean (SD) log IgE</td>
<td>0.7 (0.3)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td>Median (IQR) symptom</td>
<td>5.5 (4.0–7.0)</td>
<td>5.5 (3.5–7.0)</td>
</tr>
<tr>
<td>score</td>
<td></td>
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</tr>
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</table>

* Risk group—patients with congenital heart disease, bronchopulmonary dysplasia, or ex-premature patients.

Efficacy analysis

The efficacy of prednisolone was assessed by comparing the symptom scores of prednisolone and placebo groups. The study period included the first three days after admission, during which time the patients were treated with either prednisolone or placebo. The primary outcome measure was the change in symptom scores from day 0 to day 7. The symptom score was calculated as the sum of four specific symptoms: respiratory rate, adventitious breath sounds, skin color, and oxygen saturation. Each symptom was scored on a scale from 0 to 3, with higher scores indicating more severe symptoms.

Results

During the study period, 54 children were enrolled, with 27 in each group (prednisolone and placebo). The baseline characteristics of the patients were similar between the two groups. The median age of patients in the prednisolone group was 3.3 months (IQR: 1.4–5.9), and in the placebo group, it was 3.9 months (IQR: 1.9–6.1).

The symptom scores were calculated for each patient daily. The mean (SD) symptom score on day 0 was 5.5 (4.0–7.0) in the prednisolone group and 5.5 (3.5–7.0) in the placebo group. The mean decrease in symptom scores over the first three days was significantly greater in the prednisolone group (1.2 (0.2) points/day) compared to the placebo group (0.3 (0.2) points/day, p = 0.02). The length of time in hospital was one day shorter in the prednisolone group than in the placebo group; this difference was statistically significant (7.3 (1.2) days in the prednisolone group versus 8.3 (0.9) days in the placebo group, 95% CI for difference = −1.2 to −0.1, p = 0.02).

Figure 1 shows the median symptom scores for all non-ventilated patients (20 in the prednisolone group and 20 on placebo on day 0).
score in the first 3 days of treatment was \(-1.8\) (0.2) points/day in the prednisolone group and \(-0.8\) (0.3) points/day in the placebo group. In order to determine whether the effect of treatment was dependent on the severity of symptoms at entry we performed an analysis of variance modelling the effects of treatment, baseline severity score, and the interaction between the two. Only treatment entered the model significantly (F = 4.96, p = 0.03), whereas neither baseline severity score (F = 1.03, p = 0.31) nor the interaction term (F = 0.06, p = 0.81) contributed significantly.

Fourteen patients (seven in each group) were on mechanical ventilation at entry into the study. One girl with bronchopulmonary dysplasia died three weeks after admission as a result of respiratory failure. She had received placebo. The duration of mechanical ventilation was 1.6 days shorter in the prednisolone group (4.7 (1.1) days) than in the placebo group (6.3 (1.6) days), 95% CI for difference \(-5.8\) to 2.7, p = 0.56. None of the patients in either group needed to be reintubated due to upper respiratory tract symptoms resulting from intubation. The duration of stay in hospital was six days shorter in the prednisolone group (11.0 (0.7) days) than in the placebo group (17.0 (2.0) days), 95% CI for difference \(-10.2\) to \(-1.8\), p < 0.01.

Neither a positive family history for atopic disease nor the total IgE level of the patients at entry to the study confounded the effect of prednisolone. There was no significant difference in the duration of supplemental oxygen, the use of bronchodilators, or the proportion of patients who received antibiotics between the two groups.

**Discussion**

The results of this study suggest that systemic corticosteroids may be effective in accelerating the clinical recovery of children admitted to hospital with RSV bronchiolitis. Patients who were treated with prednisolone showed a significantly faster clinical improvement, although the beneficial effect of prednisolone was relatively small. Ventilated patients who were treated with prednisolone were admitted to hospital for a considerably shorter duration than patients in the placebo group.

Several investigators have studied the effect of corticosteroids in children with bronchiolitis, but results are inconsistent. Studies that demonstrated a beneficial effect had an inhomogeneous study population or numbers were small. Three other studies could not demonstrate a beneficial effect of corticosteroids on bronchiolitis, although none of these studies was confined to patients with microbiologically confirmed RSV bronchiolitis. This may partly explain the differences from the results of the present study and stresses the importance of strict inclusion criteria. We included only patients with RSV induced wheeze.

RSV causes most but not all cases of bronchiolitis and the inflammatory response to other pathogens may differ from that observed to RSV – that is, interferon is found in significantly lower amounts in the nasopharynx of children with RSV infections than in children with parainfluenza or influenza virus infections. Recently, De Boeck et al demonstrated no effect of corticosteroids on microbiologically confirmed RSV bronchiolitis. In this study, however, patients belonging to risk groups for severe RSV bronchiolitis were excluded because of alternative treatment. In our study there was a trend towards a greater beneficial effect of steroid therapy in more severely affected children. This trend, however, was not statistically significant. In addition, our study was not specifically designed to answer this question. The observed trend would suggest that additional studies on the effect of steroid treatment in infants with severe RSV bronchiolitis are warranted.

RSV alone is not sufficient to cause disease, and increasing evidence suggests that the immune response leading to airway inflammation contributes considerably to illness. Corticosteroids may reduce this airway inflammation. Airway inflammation in children is difficult to study. The symptom score that we and others used is obviously an insensitive method for assessing improvement in lung function. In children with a low pretreatment score the symptom score is especially less sensitive than in children with a higher pretreatment score.

Further study should focus on more sensitive measurements of airway inflammation, such as cell or cytokine profiles in bronchoalveolar lavage fluid, to measure more directly the effect of corticosteroids.

The beneficial effects of corticosteroids should be weighed against their side effects. In the present study no clinical significant side effects of prednisolone were found. This is in accordance with previous studies regarding the safety of short courses of oral steroids for asthma exacerbations and croup in children. Viral shedding may be prolonged by corticosteroids. However, the clinical and epidemiological consequences of a possible prolonged period of viral shedding in the limited group of patients who need to be admitted to hospital with severe RSV bronchiolitis are probably small.

In conclusion, this study shows that prednisolone is effective in accelerating the clinical recovery of children admitted to hospital with RSV bronchiolitis. The effect is limited and more studies are required to evaluate the role of steroid therapy in these infants.

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