

Inhaled corticosteroids during and after respiratory syncytial virus-bronchiolitis may decrease subsequent asthma

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Respiratory syncytial virus (RSV) bronchiolitis in infancy can lead to bronchial hyper-reactivity or recurrent obstructive bronchitis. The aim of the present study was to determine whether the type of treatment has an influence on respiratory status after RSV bronchiolitis. The study involved 117 infants (mean age 2.6 months), who needed hospital treatment because of RSV bronchiolitis. The patients were divided randomly into three groups. All received the same symptomatic treatment. Group I children received symptomatic treatment only, group II children were treated for 7 days with inhaled budesonide, 500 µg three times per day, administered via a nebulizer. Group III children received nebulized budesonide, 500 µg twice per day for two months. Follow-up consisted of out-patient check-ups 2 and 6 months after the infection, and telephone contact two years after the infection. Statistically significant differences were seen between the groups. In group I 37% of the children had asthma, in group II 18%, and in group III 12%. According to the present study it seems that inhaled corticosteroid treatment during and after the acute phase of infant RSV bronchiolitis may have a beneficial effect on subsequent bronchial wheezing tendency.

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Respiratory syncytial virus (RSV) is the most common cause of respiratory tract infection in infants and young children (1). The clinical presentation can vary from mild respiratory tract infection to severe bronchiolitis, but only a minority, 0.5–2% of infants, require admission to hospital (2). Acute-phase in-patient treatment of bronchiolitis has changed little in past decades (3). RSV bronchiolitis may, however, be associated with subsequent bronchial hyper-reactivity, recurrent obstructive bronchitis and asthma symptoms (4–8). This raises the question of the need to prevent such subsequent complications.

Childhood asthma is a heterogeneous condition in which several factors can trigger symptoms and atopy is strongly associated with persistence of wheeze (1). No association has been found between the incidence of RSV lower respiratory tract illnesses in early life and the

subsequent development of allergic sensitization (9). Lower respiratory tract illnesses in early life and subsequent recurrent episodes of wheezing have been reported, but the role of viral respiratory infections and the development of asthma is complex and controversial (10, 11). Certain viral infections of the immature airway may sensitize to environmental allergens (12), or viruses may cause airway damage (13) and/or cause hyper-reactivity in the bronchial tree (14). The incidence of asthma has been shown to be up to 25% in children after RSV bronchiolitis (4, 15). Few studies present the role of inhaled steroids in the prevention of recurrent wheezing after acute viral bronchiolitis (16–19). The aim of the present study was to determine whether the type of bronchiolitis treatment in small infants during and after the acute phase of RSV infection influences the subsequent respiratory status.

Patients and methods

Patients

This open study comprised 117 consecutive infants, 0–9 months of age (mean age 2.6 months), needing hospital treatment because of RSV bronchiolitis. The diagnosis of bronchiolitis was based on the clinical presentation of breathing difficulties, tachypnea (a respiratory rate > 40 /min), chest retraction and auscultation of bilateral crackles with or without wheezing. The viral identification of RSV was based on nasopharyngeal secretions using immunofluorescent techniques.

All children were healthy, full-term babies without chronic disease. Any infant requiring mechanical ventilation was excluded. Preterm babies were excluded because of the possible respiratory problems associated with prematurity. One preterm child was accidentally randomized to the study but subsequently excluded. The infants were divided randomly into the study groups.

The symptomatic treatment was equal in all infants. Extra oxygen was administered if the arterial saturation with pulse oximeter was below 95%. The need for extra oxygen did not exceed 1–2 days and there were no differences between the groups. Symptomatic treatment consisted of inhaled nebulized bronchodilators and inhaled racemic epinephrine. Extra oxygen was given if arterial saturation was below 95%. The symptomatic treatment did not include steroids in any form.

Follow-up for two years was completed in 109 children.

Groups

Group I ($n=41$; $n=38$ at the two-year follow-up, three children lost to follow-up). The children received only symptomatic treatment, namely oxygen, bronchodilators and/or racemic epinephrine by inhalation.

Group II ($n=40$; $n=39$ at the two-year follow-up, one child excluded because of reinfection with RSV). The children had the same symptomatic treatment, but also treatment with inhaled budesonide (Pulmicort; Astra, Kirkkonummi, Finland) for seven days, 500 μg t.i.d. using a Spira nebulizer (Hengityshoitokeskus, Hämeenlinna, Finland).

Group III ($n=36$; $n=32$ at the two-year follow-up, four children excluded, one because of prematurity and three because of incomplete medication at home). The children received similar symptomatic treatment and additional inhalation treat-

ment with budesonide, 500 μg b.i.d. by means of a nebulizer, for two months.

Follow-up

Follow-up consisted of out-patient check-ups 2 and 6 months after the infection. After that the children were not under control of the investigators. At two months' check-up the clinical status was recorded and at six months' check-up skin-prick tests for cow's milk, egg, fish, wheat, *Dermatophagoides pteronyssinus*, dog and cat epithelium, and birch were carried out. A positive control test was conducted using histamine chloride (1 mg/ml), and a negative control test using saline. Standardized extracts were used (ALK, Copenhagen, Denmark). A wheal diameter exceeding 3 mm was regarded as positive.

The child was defined as atopic when: (i) atopic eczema was diagnosed by a physician; or (ii) the result of at least one skin-prick test was positive combined with a history of food allergy; or (iii) the skin of the infant was dry and scaly together with at least one positive skin-prick test. Atopic heredity was positive when asthma, allergic rhinitis or atopic dermatitis was diagnosed by a doctor in one or both parents. The check-up two years after the infection was carried out as a structured telephone interview. Respiratory status was recorded as asthmatic when anti-inflammatory asthma medication was continuously used. In Finland infant asthma diagnosis in children under three years of age is settled at the third bronchial obstructive period demanding hospital care.

Statistical methods

Outcomes in the different groups were cross-tabulated, and differences between groups were tested by calculating odds ratios (OR) of 2×2 tables, using the BMDP (BioMedical Data Processing) program 4F. Confidence intervals (CI) were calculated using the standard errors of $\ln$ (OR).

Ethics

The study was approved by the Human Research Ethics Committee of the Helsinki University Central Hospital. All families were given oral and written information and they gave written consent before enrolment in the study.

Results

Differences and similarities between the child groups

The backgrounds of the groups revealed no significant differences regarding age at time of bronchiolitis, duration of breast feeding or smoking at home. Data on smoking during pregnancy was not obtained.

Group I

Atopic heredity was recorded in 29% of the children. The age range was from 0.5 months to 5.2 months. Smoking at home was recorded in 16% of cases. The mean duration of breast feeding was 4.0 months.

Group II

Atopic heredity was recorded in 49% of the children. The age range was from 0.3 months to 6.4 months. Smoking at home was recorded in 8% of cases. The mean duration of breast feeding was 4.4 months.

Group III

Atopic heredity was recorded in 44% of the children. The age range was from 0.5 months to 5.9 months. Smoking at home was recorded in 13% of cases. The mean duration of breast feeding was 4.2 months.

The respiratory status after RSV bronchiolitis

The check-up 2 years after RSV bronchiolitis in infancy revealed that 25% of all children in the study had continuous asthma inhalation therapy. Thirteen per cent of Group I children were recorded as atopic, 28% of Group II children, and 25% of Group III children (Fig. 1.).

Figure 1 shows the distribution of atopic heredity, the atopy of the children and the distribution of asthma inhalation therapy in the study groups. The atopic status of the child was recorded 6 months after RSV infection. There were differences in the outbreaks of asthma between the groups (Fig. 2.).

Two years after the infection, in Group I (symptomatic treatment), 14 of 38 children (37%) were receiving asthma medication, compared with Group II (one week of budesonide treatment), in which 7 of 39 children (18%) were receiving asthma inhalation treatment ($p = 0.006$). In Group III (2 months of budesonide inhalation therapy) 4 of 32 children (12%) were receiving asthma inhalation therapy ($p = 0.01$ compared with Group I).

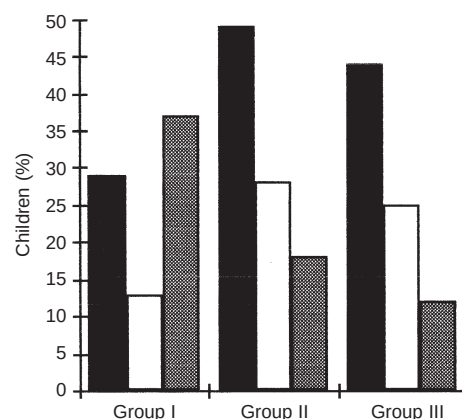


Fig. 1. The distribution of atopic heredity, the child's own atopy and asthma in patient groups I, II and III. Atopic status was recorded at 6 months after respiratory syncytial virus infection. Positive atopic heredity was defined when asthma, allergic rhinitis or atopic dermatitis was diagnosed by a doctor in one or both parents. Black bars, heredity; white bars, atopy; grey bars, asthma.

Comparison between Group I and Group III yielded an OR of 4.08 (95% CI 1.39–11.98), i.e. there was a significant difference. When combining Groups II and III, the OR was 3.18 (95% CI 1.25–8.12). The OR for Group II, 2.67, was almost significant (95% CI 0.98–7.27). At the 90% level the CI was 1.15–6.19.

Discussion

The results of this prospective randomized study indicate that inhaled budesonide therapy after RSV bronchiolitis may reduce respiratory symptoms during the next 2 years. Two months of budesonide inhalation resulted in a reduced need for asthma treatment 2 years after RSV bronchiolitis. Even 1 week of inhaled budesonide three times a day seemed to have a favorable outcome 2 years after infection compared with children who received only symptomatic treatment. The degree of benefit was not related to the atopic status in infancy or atopy heredity of the children. On the contrary, atopic heredity and atopy were even more common in the Groups II and III compared with Group I with no treatment.

It is not clear whether increased airway sensitivity is present before bronchiolitis or whether it is a consequence of infection. Infection with RSV and other respiratory viruses may result in wheezing at the time of infection and thereafter an increased incidence of asthma has been observed in children who had bronchiolitis during infancy (15). In children with a history of bronchiolitis by the age of 2 years the incidence of asthma at 2 years of age has been reported to be 44% (20).

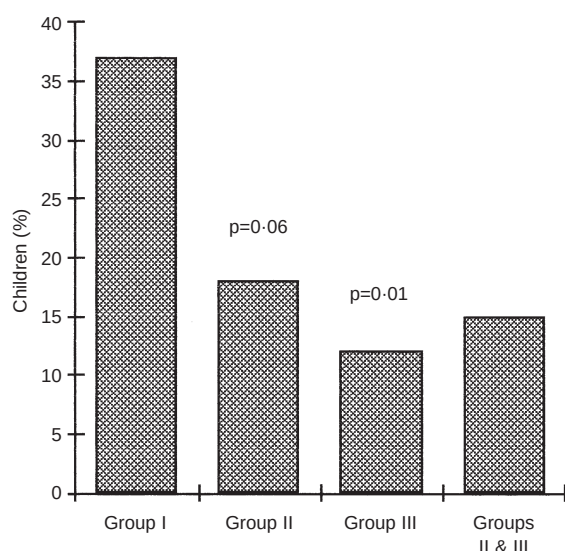


Fig. 2. The percentages of children on continuous medication for asthma, as evaluated two years after respiratory syncytial virus-bronchiolitis in infancy. The study groups were initially formed prospectively in randomized fashion. Group I: control, symptomatic. Group II: budesonide 500 µg × 3, 7 days. Group III: budesonide 500 µg × 2, 2 months. Difference for asthma between group I and group II: $p = 0.06$. Difference for asthma between group I and group III: $p = 0.01$.

The relationship between infections and asthmatic hyper-reactivity is complex and controversial. Infantile wheezing types have been categorized by Martinez et al. (21). One group exhibits abnormal pulmonary function without atopy. These are transient wheezers. The second group consists of atopic early onset wheezers, in whom wheezing continues after 3 years of age, and in whom there is early onset of asthma. The third group consists of asthmatics who are atopic and start wheezing after 3 years of age.

Wheezing lower respiratory illness associated with atopy may also present in children with increased responsiveness to histamine and tendency to obstructive symptoms that persist into later childhood (22). RSV lower respiratory tract infection and atopic status seem to be independent risk factors for the subsequent development of persistent wheezing (9).

The role of smoke exposure during infancy and during pregnancy can be an important determinant of lung function and can influence upon the future respiratory status of the child. In our present study smoking habits of the families did not differ between study groups but information of maternal smoking during pregnancy was not obtained. The use of systemic corticosteroids does not seem to affect the rate of clinical improvement in acute-phase bronchiolitis (23, 24). There are controversial reports

concerning inhaled corticosteroid therapy; evidence of prolonged positive effects after inhaled nebulized steroid therapy have been documented (16–18, 25) but opposite results are concluded according to other studies (19, 26).

The inhalation techniques and the inhalation delivery system may be of importance. Using the medication in a nebulized form is perhaps superior compared with aerosol spacers, especially in small children.

The time of starting inhaled steroids may also be of importance. In our study the inhalation therapy was started immediately after diagnosis and even the short, 1-week intensive therapy seemed to have a favorable effect compared with the control group.

The present study indicates the possibility of positive effect of steroid inhalation therapy in RSV-bronchiolitis in early infancy. We advocate the use of inhaled budesonide in nebulized form during and after RSV bronchiolitis in small infants, in order to reduce the incidence of subsequent respiratory symptoms in the near future. However, the best and sufficient length of the treatment period, as well as the dose of the inhaled steroid, need to be determined. Also, should we choose possible risk-babies or give medication to all infants? Further double-blind studies are required to solve the relationship between bronchiolitis and subsequent childhood asthma.

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