Concomitant Chronic Sinusitis Treatment in Children With Mild Asthma*

The Effect on Bronchial Hyperresponsiveness

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Study objective: Previous studies have suggested that aggressive treatment of sinusitis can decrease bronchial hyperresponsiveness (BHR). However, there is still too little evidence to draw this conclusion, and the concept remains controversial.

Design: A prospective, open-label study.

Setting: University children’s hospital allergy and immunology center and radiologic department.

Patients: Sixty-one children with mild asthma and allergic rhinitis participated in the study. Forty-one of these 61 children had sinusitis, and the remainder had no sinusitis. Ten matched, nonatopic, healthy children were used as a control group.

Intervention: Children with chronic sinusitis were placed into two groups. One group was treated with amoxicillin-clavulanate for 6 weeks and then with nasal saline solution irrigation for 6 weeks. For the other group, the treatment order was reversed. Children without chronic sinusitis received nasal saline solution irrigation for 12 weeks.

Measurements: Clinical symptoms and signs of sinusitis, FEV₁, and BHR were analyzed in the patients before and after treatment.

Results: The clinical symptoms and signs of sinusitis, but not FEV₁, showed a significant improvement after antibiotic treatment. After aggressive treatment for sinusitis, it was found that the provocative concentration of methacholine causing a 20% fall in FEV₁ of children with mild asthma and sinusitis was significantly higher after treatment.

Conclusion: The results suggest that every asthmatic patient needs to carefully evaluate to determine whether the patient has concomitant sinusitis. Respiratory infections that meet criteria for sinusitis, even if they do not exacerbate asthma, should be treated. It is suggested that sinusitis should always be kept in mind as a possible inducible factor for BHR, and that aggressive treatment of chronic sinusitis is indicated when dealing with an asthmatic patient who shows an unpredictable response to appropriate treatment. Moreover, the findings of this study provide more evidence for an association between sinusitis and asthma with respect to BHR.

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Key words: asthma; bronchial hyperresponsiveness; methacholine challenge test; sinusitis

Abbreviations: BHR = bronchial hyperresponsiveness; PC₂₀ = provocation concentration of methacholine causing a 20% fall in FEV₁

Bronchial hyperresponsiveness (BHR), defined as an exaggerated constrictive response of the airways to a wide variety of stimuli, is caused by the characteristic pathologic abnormalities seen in asthma, and BHR clearly plays a central role in the pathophysiology of asthma.¹ It is present in almost all patients with current symptomatic asthma.² The frequent association of asthma and sinusitis has been noted for many years. As many as 80 to 90% of children and adolescents with asthma also have nasal
symptoms, and half of all patients with asthma have radiographic evidence of sinusitis. Several studies have described the incidence of chronic sinusitis to be as high as 40 to 60% in children with bronchial asthma. In Taiwan, 10.4% of children have an asthmatic disease, and half of them also have concomitant sinusitis.

Corren and Rachelefsky suggested that inflammation of the upper airway, as from allergic rhinitis or sinusitis, results in increased bronchoconstriction of the lower airway. In 1870, Kratchmer first suggested, on the basis of an animal model, that chemical stimulation of upper airway mucosa may induce bronchoconstriction. Bucca et al reported that increased lower airway responsiveness is associated with chronic sinusitis and that BHR improved after sinusitis therapy. Rachelefsky et al showed that aggressive medical treatment of concomitant chronic sinus disease in asthmatic children notably improved the asthmatic symptoms and lung function. Another study involving surgical treatment of chronic sinusitis also showed similar results. These findings suggest that concomitant chronic sinusitis is a precipitating factor for bronchial asthma or lower inflammatory airway diseases. However, there continues to be a poor appreciation of this, and indeed some doubt as to whether sinusitis does play a causative role in asthma. Whether the two diseases are linked by a cause-and-effect relationship or as a result of pathogenetic events affecting the whole respiratory tract remains unanswered.

It is still unknown whether chronic sinusitis itself induces BHR, or even whether there is a difference in BHR between chronic sinusitis, allergic rhinitis, or other bronchial diseases. Current studies are promising, but as yet there is insufficient evidence to draw a final conclusion.

The relationship between upper airway infection and BHR thus remains incompletely investigated. The idea of clarifying the relationship between sinusitis and asthma, together with a study of whether aggressive treatment of chronic sinusitis is indicated, is an attractive one. In this prospective study, the aim was to determine, firstly, whether aggressive treatment of sinusitis can improve the care of asthmatic patients and, secondly, whether chronic sinusitis itself induces BHR.

Subjects and Methods

Study Subjects

A prospective, open-label study was conducted to evaluate the difference in BHR of asthmatic children with chronic sinusitis before and after their concomitant sinusitis was treated. Sixty-one children with mild asthma (asthma history range, 1 to 9 years; age range, 7 to 12 years) and 10 age-matched healthy children were included in this study at Chung Gung Children’s Hospital during from 1999 to 2000. All the asthmatic children were mite sensitive (Dermatophagoides pteronyssinus and Dermatophagoides farinae) in terms of having a positive history of asthma attack during house cleaning, a skin test response > 2+ (wheal twice as large as control; erythema > 20 mm) by the intracutaneous route with mite extract at a concentration of 10^-5 g/mL, and a positive mite radioallergosorbent test result (CAP System; Pharmacia Upjohn Diagnostics; Uppsala, Sweden). The diagnosis and classification of the clinical severity of asthma was made according to National Asthma Education and Prevention Program. All subjects had occasional symptoms including variable wheezing and coughing controlled only by β2-agonists. These asthmatic patients also had intermittent perennial allergic rhinitis concomitantly. None of them had acute exacerbations of asthma during the study period. Healthy children without any clinical history of allergic rhinitis, chronic coughing, asthma, or sinusitis served as the control group.

Radiologic Examination

Skull radiographs were obtained in three views: frontonasal (Caldwell), nasomental (Waters), and lateral views. Chronic sinusitis was defined as chronic inflammation of nasal mucosa and para nasal sinus mucosa with the following: (1) persistent symptoms and signs of sinusitis for > 12 weeks, including nasal obstruction, headache, and postnasal drainage; and (2) complete opacification or the appearance of fluid in one or both maxillary sinuses and ethmoid cells in the plain sinus radiographs. These findings were further confirmed by modified and limited prone coronal CT scans of selected maxillary, sphenoidal, and frontal ethmoidal sinuses, with a slice thickness of 3 mm in accordance with our previous report to minimize radiation doses and avoid superimposition of structures, while allowing very accurate resolution of the sinus mucosa. Asthmatic children who had normal findings in the maxillary, sphenoidal, ethmoidal, and frontal sinuses were also evaluated with CT, and were grouped as patients without sinusitis. In the control group, CT was not carried out for ethical reasons.

The Human Research Committee approved this project. Informed consent was obtained from the patients’ parents or guardians prior to commencement of the study.

Patients were studied outside of allergen exposure and needed to have had no respiratory tract infection for at least the previous month. To exclude the impact of viral infection on the imaging clinical evaluation, and airway hyperresponsiveness, all subjects were evaluated for common upper airway viral infection as they were enrolled into the study and before performing the CT scan. This was detected by centrifugation-enhanced shell vial culture followed by fluorescent staining with monoclonal antibodies from nasopharyngeal secretions. This technique rapidly detects and identifies respiratory tract virus within 24 h. These viruses included respiratory syncytial virus; adenovirus; parainfluenza virus types 1, 2, and 3; and influenza virus A and B. Patients were excluded if the result was positive before enrolling in the study.

Study Design

Forty-one children with intermittent perennial allergic rhinitis and mild asthma concomitant sinusitis were sequentially assigned to either group A or group B according to the sequence of their enrollment in this study. In group A, 20 of the 41 patients with sinusitis received 6 weeks of treatment for chronic sinusitis on diagnosis of sinusitis. In group B, 21 of the 41 patients with
sinusitis were not treated for sinusitis, except with an intranasal saline solution irrigation every week for the first 6 weeks. After this initial period, group B patients received 6 weeks of treatment for chronic sinusitis. Group C contained 20 asthmatic children with perennial allergic rhinitis without sinusitis. None of the patients with asthma received inhaled cromoglycate or corticosteroids therapy during the study period. Group D consisted of 10 healthy children who served as the control group (Fig 1).

The antibiotic, amoxicillin-clavulanate, which has mixed aerobic and anerobic Gram-positive coverage, and with an indication for sinusitis on diagnosis of sinusitis,19,20 The regimens for the treatment of sinusitis were as follows: (1) intranasal saline solution irrigation every week for relieving the nasal blockage and mucopurulent rhinorrhea, and (2) amoxicillin-clavulanate, 40 mg/kg/d for 6 weeks. Children with normal radiographic findings (groups C and D) were only treated with intranasal saline solution irrigation every week for 12 weeks.

**Methacholine Challenge Tests**

Bronchial challenge tests21 were performed in accordance with the modified method of Chai et al.22 Baseline lung function was measured, and a dose of saline solution was used as a control.

![Diagram of study design for the treatment for sinusitis and the methacholine challenge tests.](image-url)

**Data Analysis**

All PC20 values were log 10 transformed before statistical analysis and reported as a geometric mean and a geometric SEM. FEV1, at the beginning and end of the study, was expressed as the geometric mean and SD values. Differences within groups, comparing the test result before and after the 6 weeks of treatment, were assessed with the Wilcoxon signed-rank test, including the symptoms and signs of chronic sinusitis. Kruskal-Wallis variance analysis was used for comparison of the four groups at the same time point with regard to FEV1 and PC20 values. Values < 0.05 were considered to be statistically significant. The statistical significance was as two-tailed tests.

**Results**

Sixty-one children with mild asthma and allergic rhinitis (40 male and 21 female; mean age ± SD, 8.8 ± 1.5 years) and 10 nonatopic healthy children (7 male and 3 female; mean age, 8.8 ± 1.5 years) participating in the study were followed up regularly at the Allergy Clinic, Department of Pediatrics, Chung Gung Children’s Hospital during the study period. All patients in these four study groups were similar for age, weight, and height.

All the asthmatic patients with sinusitis in groups A and B (12 male and 8 female; mean age, 8.8 ± 1.5 years; and 14 male and 7 female; mean age, 8.7 ± 1.7 years, respectively), but not group C (14 male and 6 female; mean age, 9.0 ± 1.4 years) had clinical symp-
toms and signs of sinusitis (headache, nasal purulent discharge, and postnasal drainage) before the sinusitis was treated (Table 1). These symptoms and signs of sinusitis disappeared after treatment, and the number of patients with a nocturnal cough were also markedly reduced (Table 1). There is a statistically significant difference before and after the use of antibiotics for treatment regarding almost all symptoms and signs of sinusitis. However, in group B, there was also statistical differences in postnasal drainage, nasal congestion, and nocturnal cough when only nasal saline solution irrigation was used to treat sinusitis. Generally speaking, when antibiotics are used to treat associated sinusitis in asthmatic patients, the symptoms are significantly improved. The pulmonary functions of each group during the study period are summarized in Table 2. A significantly lower baseline FEV₁ (84.3 ± 7.0% predicted in the 61 patients) was observed compared to patients in the group D (control) [FEV₁, 108.9 ± 2.1% predicted]. There was no difference between FEV₁ values before and after treatment of sinusitis for each asthma group (Table 2).

All 71 patients completed the methacholine inhalation challenge test safely and were monitored for at least 1 h after the test. PC<sub>20</sub> values for all patients are shown in Figures 2–4. Geometric mean ± SEM PC<sub>20</sub> values at the beginning of treatment for sinusitis showed no significant difference between group A (3.68 ± 0.52 mg/mL), group B (3.11 ± 0.45 mg/mL), and group C (2.98 ± 0.43 mg/mL). Three of 20 patients in group A, 3 of 21 patients in group B, and 2 of 20 patients in group C did not show a positive lower airway hyperresponsiveness (the FEV₁ had not decreased by 20% with a concentration of methacholine ≥ 8 mg/mL in these 8 patients). PC<sub>20</sub> values in asthmatic children with concomitant sinusitis after treatment of the sinusitis were significantly higher than before antibiotic treatment (mean ± SEM, 3.68 ± 0.52 mg/mL vs 7.31 ± 0.98 mg/mL in group A; 3.11 ± 0.45 mg/mL vs 7.00 ± 0.90 mg/mL in group B). In comparison with the pretreatment of sinusitis, both groups A and B showed a significant improvement of BHR after 6 weeks of therapy for chronic sinusitis (p < 0.001 and 0.001, respectively). PC<sub>20</sub> values of children with normal radiographic findings (group C and D) who were only treated with intranasal saline solution irrigation every week for 12 weeks did not change significantly from the baseline throughout the study.

**DISCUSSION**

BHR has been taken as a sign of airway inflammation. It is not, however, specific to asthma and has

### Table 1—Number of Patients With Clinical Symptoms and Signs of Sinusitis, and Nocturnal Coughing Before (Baseline) and After the Sixth Week and 12th Week of Treatment for Sinusitis

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Group A (n = 20)</th>
<th>Baseline</th>
<th>Sixth Week</th>
<th>12th Week</th>
<th>Group B (n = 21)</th>
<th>Baseline</th>
<th>Sixth Week</th>
<th>12th Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mucopurulent rhinorrhea</td>
<td></td>
<td>10</td>
<td>0*</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postnasal drainage</td>
<td></td>
<td>8</td>
<td>0*</td>
<td>0</td>
<td>16</td>
<td>4*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td></td>
<td>18</td>
<td>2*</td>
<td>0</td>
<td>18</td>
<td>12†</td>
<td>4*</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
<td>8</td>
<td>0*</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nocturnal cough</td>
<td></td>
<td>15</td>
<td>2*</td>
<td>0</td>
<td>18</td>
<td>12†</td>
<td>4*</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.01 compared with respective previous value.
†p < 0.05 compared with respective previous value.

### Table 2—FEV₁ Percentage of Predicted of Asthmatic Children With Sinusitis (Groups A, B), Asthmatic Children Without Sinusitis (Group C), and Healthy Children (Group D)

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>84.1 ± 6.4</td>
<td>84.6 ± 7.2</td>
<td>84.3 ± 7.4</td>
<td>108.9 ± 2.1</td>
</tr>
<tr>
<td>Sixth week</td>
<td>85.3 ± 10.2</td>
<td>83.2 ± 8.1</td>
<td>86.7 ± 6.8</td>
<td>106.0 ± 6.2</td>
</tr>
<tr>
<td>12th week</td>
<td>85.3 ± 8.0</td>
<td>84.3 ± 6.2</td>
<td>86.7 ± 6.8</td>
<td>106.0 ± 6.2</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
been described in patients with allergic rhinitis, cystic fibrosis, COPD, and chronic sinusitis.

Despite observations of an association between sinusitis and asthma, a direct cause and effect relationship remains to be established. It has been observed that treatment of sinusitis may improve the course of asthma. However, these observations are anecdotal or from uncontrolled studies. This prospective study was designed to decipher this epiphenomenon and/or causal association.

Early studies have suggested that sinusitis is more common in allergic individuals than in control subjects. Abnormal radiologic examinations of paranasal sinuses were frequently found in children with asthma and/or allergic sinusitis. In this study, all the asthmatic patients had had clinical manifestations of sinusitis for >12 weeks. CT of the paranasal sinuses has thus emerged as a reliable and standard test for the assessment of chronic sinusitis. To increase the accuracy of the diagnosis of sinusitis and to reduce the radiation dose related to the sinus CT images, modified and limited prone coronal CT at selective maxillary, sphenoidal, and fronto-ethmoidal sinuses was used to clarify whether asthmatic patients and normal control subjects had sinus disease.

Viral airway infections may induce BHR during and following the infection. Moreover, as many as 87% of patients with viral rhinosinusitis have been shown to have sinus abnormalities on CT scans within 96 h. All the cases in the study were tested by centrifugation-enhanced shell vials culture tests followed by fluorescent staining with monoclonal antibodies of their nasopharyngeal secretions to exclude viral factors from the study. Since we cannot totally exclude the possibility of other viral pathogens, such as rhinovirus, patients with symptoms of respiratory tract infection within the previous 1 month were not enrolled.

Evidence of lower airway hyperresponsiveness to a number of provocative agents can be found in between 15% and 56% of individuals who have only allergic rhinitis. An experimental study has suggested that inflammation of the upper airway, as occurs with allergic rhinitis or sinusitis, increases bronchoconstriction in the lower airway. Watson et al demonstrated that airway responsiveness to methacholine was significantly reduced after intranasal beclomethasone treatment. However, several investigators have shown no alteration in lower airway function in patients with allergic rhinitis and asthma when they perform nasal provocation with antigen or histamine. All of asthmatic patients in this study also had allergic rhinitis. To reduce the influence of any treatment of the sinus disease on airway responsiveness, the patients did not receive any systemic or intranasal corticosteroids therapy during the study period. Significantly, the study of Oliveira et al revealed that treatment of allergic rhinitis itself did not improve the BHR of asthmatic patients. Therefore, it is likely that the influence of concomitant allergic rhinitis on the result of BHR in this study would be quite small.

The use of intranasal saline solution irrigation every week was used to try and relieve nasal blockages and remove nasal mucopurulent rhinorrhea, particularly in the group B patients who did not receive any antibiotic therapy during the initial 6 weeks. In fact, repeated daily warm saline solution irrigation favorably affects mucociliary clearance. Nasal saline solution irrigation facilitates mechanical removal of intranasal crusts, thereby improving patient comfort and improving drainage. The tonicity may also play a role in decreasing mucosal edema, and this contributes to an improvement in nasal congestion for most of these patients. However, nasal saline solution irrigation alone cannot improve...
BHR in patients with mild asthma associated with allergic rhinitis without sinusitis. The results from this study were similar to that of Oliveira et al.13 Besides, comparing the BHR before and after antibiotic treatment, it was also found that for those asthmatic patients with associated allergic rhinitis and sinusitis, nasal washing does relatively little, whereas antibiotic treatment does result in a significant improvement. A comparison for group B of the geometric mean ± SEM PC_{20} values between the beginning and after 6 weeks duration of treatment with intranasal saline solution irrigation showed no significant difference (3.11 ± 0.45 mg/mL vs 3.72 ± 0.83 mg/mL). Thus we suggest that intranasal saline solution irrigation can be used for symptom relief in these patients throughout this study without any influence on BHR.

The symptoms and signs of sinusitis disappeared after treatment, and the number of patients with nocturnal cough was also markedly reduced (Table 1). These findings are similar to the results of Rachelefsky et al10 and Oliveira et al.13 In contrast with previous reports, there was no difference in FEV_{1} values before and after the treatment of sinusitis for each asthma group in the study (Table 2).13,40,41 This might be due to the fact that the patients enrolled had only mild asthma, unlike the subjects of the previous reports. However, Manning et al42 also failed to find a significant change in pulmonary function scores in pediatric patients with asthma after surgical treatment for chronic sinusitis.

It has been demonstrated that inhaled steroids improve direct and indirect BHR to different degrees and at different rates. This might contribute to the 13.1% of 61 patients with mild asthma who had normal PC_{20} values before the treatment for sinusitis. The high reproducibility of the PC_{20} measurements in subjects with mild, stable asthma was confirmed by Inman et al.43 In this study, compared to pretreatment of sinusitis only, both groups A and B showed significant improvements in BHR after 6 weeks of antibiotic therapy for chronic sinusitis. A recent report from Oliveira et al13 also showed that children with allergic rhinitis and sinusitis with asthma had improved BHR to methacholine, and their symptoms were decreased after appropriate treatment for sinusitis.

Both the decreased clinical symptoms and signs, and the improvement in BHR after treatment of the concomitant sinusitis may result from multiple factors. The possible mechanisms include a reduction in the mechanical aspiration of sinus mucopurulents into the lower airway and a resulting reduction in the nasobronchial reflex,44,45 a reduction in chemotactic mediators,46 and an improvement in the β-adrenergic responsiveness in the lower airway.47

Bucca et al9 reported extrathoracic airway hyperresponsiveness and BHR in adult patients with chronic sinusitis increased during acute exacerbation and significantly decreased after treatment. This shows that airway hyperresponsiveness in patients with sinusitis may be triggered by seeding of the inflammatory process into the pharynx from the affected sinuses. An improvement in sinus diseases may also improve lower airway inflammation and result in a reduction in hyperresponsiveness. The results of this study partly elucidate the close relationship between airway inflammation of the upper and lower respiratory tract.

Further evidence is presented that upper airway disease is an important component in allergic asthma diseases. This is not only true in severe asthma,48 as observed in previous literature, but also in patients with mild asthma from this study. It can be surmised that sinusitis might be implicated in the mechanism that “turns the BHR switch on” in asthmatics.

One goal of asthma treatment is to abolish the underlying airway inflammation known to be associated with this condition. However, the degree of BHR has been shown to have a correlation with the severity of the asthmatic symptoms.34,49 On the basis of the results obtained in the present study, we suggested that respiratory infections that meet the criteria for sinusitis should be treated even if they do not exacerbate the asthma.

**Conclusion**

This study confirms that the BHR of asthmatic children can be significantly improved after the concomitant sinusitis is treated. It is suggested that every asthmatic patient needs to be carefully evaluated to determine whether the patient has concomitant sinusitis.

The level of BHR may not only reflect the state of airways as a marker for airway dysfunction, but may also predict the persistent prognosis of the disease. We think that sinusitis should always be kept in mind as a possible factor inducing BHR and that aggressive treatment of chronic sinusitis is indicated when dealing with an asthmatic patient who shows an unpredictable response to appropriate treatment. Further, in addition to improving the care and prognosis of asthmatic patients, the findings also support the association between sinusitis and asthma concerning BHR.

**References**

1 Peat JK, Salome CM, Sedgwick CS, et al. A prospective study of bronchial hyperresponsiveness and respiratory symptoms