FEV1-REVERSIBILITY IN HOUSE-DUST IMMUNOTHERAPY COMPARED WITH INHALED CORTICOSTEROID IN THE TREATMENT OF CHILDHOOD ASTHMA

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ABSTRACT

Asthma is a chronic inflammatory disease of the airway. Corticosteroid is the drug of choice to control the inflammation, and prevent the development of airway hyper responsiveness and later airway remodeling. House dust immunotherapy has been shown to be effective in patients with asthma, and also in those who do not respond well to standard drug therapy. Whether immunotherapy is as effective as inhaled corticosteroid need to be studied. The objective of this study is to investigate the ability of house dust immunotherapy to improve clinical index in children with asthma, and to compare its efficacy with inhaled corticosteroid. We evaluated the beneficial effect of house dust immunotherapy in 24 asthmatic children based on the value of FEV1 reversibility before and after treatment, and also compared its efficacy to the inhaled corticosteroid. All the patients were sensitive to house dust allergen. Twenty-four children (group I) treated with house-dust immunotherapy subcutaneously, once a week for 14 weeks, and group II treated with inhaled budesonide 100-200 µg once daily. The result of Wilcoxon Signed Rank Test showed there was a significant improvement between FEV1 reversibility test before and after house-dust immunotherapy (p=0.0001). Analysis with t-test also revealed that the efficacy of house dust immunotherapy did not differ from inhaled budesonide (p=0.872). In conclusion house dust immunotherapy has been shown to be as effective as inhaled corticosteroid in improving clinical outcome in the term of FEV1-reversibility in the treatment of childhood asthma.

Keywords: Childhood asthma, house dust immunotherapy, inhaled corticosteroid, FEV1 reversibility

INTRODUCTION

Atopic asthma is an inflammatory disorder of the airways that is characterized by eosinophilic inflammation, bronchial hyper-responsiveness, intermittent airflow obstruction, and elevated immunoglobulin (Ig) E levels. However, the incidence of allergic asthma is increasing with house dust mite as an important source of perennial allergens. Bronchial hyper-responsiveness as consequence of bronchial inflammation is a functional hallmark of asthma. It can be used as a marker of inflammatory activity of these studies. Therapeutic options for the treatment of asthma have been essentially unchanged, with the exception of leukotriene modifiers, for over two decades. None of these therapeutic agents is curative or induces remission of chronic asthma. Specific allergen immunotherapy and allergen avoidance are the only treatments that modify the natural history of allergic disease, inducing a remission or long-term cure in some individuals (Cohen 1999; Abba 2003).

Specific allergen immunotherapy reduced allergen-specific bronchial hyper-reactivity and minimized increases in nonspecific bronchial hyper-reactivity (Bradding 1995). Symptoms associated with allergen triggers, irritants, cold, and exercise are all expected to improve. Prevention of airway disease progression: a prophylactic strategy using allergen immunotherapy to treat the united airway inflammation. Forty percent to 50% of persons with allergic rhinitis have concomitant asthma and 60% to 78% of subjects with asthma have allergic rhinitis. Eighty-seven percent of the subjects diagnosed with asthma developed allergic rhinitis within 2 years (35% of the total population). Of the 40% of subjects who initially developed allergic rhinitis, asthma was diagnosed in 75% within 2 years (Ilopoulos 1991). A 23-year follow up study of college students showed that the risk for developing asthma in subjects with allergic rhinitis is approximately threefold higher compared with healthy controls (Humbert 1999, Freeman 1994). The aim of this study is to investigate the ability of house dust immunotherapy to improve clinical index in children with asthma, and to compare its efficacy with inhaled corticosteroid (Budesonide).
MATERIALS AND METHODS

Study Design

The study design was controlled trial in the outpatient clinic of Allergy-Immunology Division of Dr. Soetomo Hospital from August 2004 to January 2005. Inclusion criteria were as follows: a clinical diagnosis of bronchial asthma as based on standard criteria (onset < 2 years), symptoms of wheezing / cough / dypsnea / chest discomfort / night awakening (at least 1 symptom in the last 3 months), a positive skin-prick test (mean weal diameter 5 mm at 15 minutes) to house-dust extract and/or mite (Dermatophagoides pteronyssinus and/or Dermatophagoides farinae), symptoms of asthma after house-dust exposure, a positive bronchoconstriction reversibility test, an increase in reversibility of forced expiratory volume in one second (FEV₁ reversibility) of 12% or more after administration inhaled Albuterol, and age 6-14 years. Patients with one or more of the following conditions were excluded: severe instable asthma (FEV₁ pre bronchodilator < 60% predicted normal value and FEV₁ post bronchodilator< 80% predicted normal value), the symptoms of asthma of more than 2 years, long-term therapy of glucocorticoid or others immunosupressant, concomitant disease such as active TBC, Congenital Heart Disease, therapy of glucocorticoid (inhalant/oral) of more than 30 days in 1 year or glucocorticoid injection of more than once in 1 year in the last 2 years before the first visit.

Protocol

Every child aged 6 to 14 year-old who fulfilled inclusion criteria was included in this study. The history, physical, and Lung Function Test were performed in every sample. Anti-asthmatic medication remained unchanged for the entire study period in both the steroid and the immunotherapy groups. In the first 3 months subcutaneous injections were given in weekly, and the maintenance dose was then given in intervals of 3 weeks for about 3 months. The first group received inhalation of Budesonide 100-200µg twice daily. At each visit patients were interviewed about their asthma symptoms, and local and/or systemic reactions after the previous injection. After allergen injection, patients had to stay at the outpatient clinic for at least 30 minutes, and signs and symptoms of systemic reactions as well as the diameter of the local weal and flare were recorded.

Lung Function Test was done in every week during 6 months of visit in Laboratory of Allergy-Immunology Division Department of Child Health Dr.Soetomo Hospital Surabaya. Daily recording of clinical manifestation, side effects that may occurred due to house-dust immunotherapy, and weekly Lung Function Test were done until the end of the study. Patient who did not control more than twice during follow up was declared dropped-out.

Ethical Approval

Dr.Soetomo Hospital Ethic Committee has approved this research to be performed on children using the appropriate protocol.

Sample Size and Statistical Analysis

Samples were obtained by randomization of every two subsequent patients. Estimated size of sample in this study calculated according to standard formula was 18 for every group. Therefore 49 patients that included in our study as samples had fulfilled the requirement to be analyzed. T-test was used to compare the reversibility of FEV₁ in both groups and Mann Whitney was used to analyze the clinical improvement between two groups. The values were presented in mean and standard deviation, p value of less than 0.05 was considered significant. Analysis performed using SPSS for Windows version 12.0.

RESULTS

Fifty-six children who were diagnosed as Asthma Bronchiale elrolled in this study. Finally, 49 children particiapated in this study, and then divided into steroid (25 children) and immunotherapy groups (24 children). The average of age for steroid (group 1) and immunotherapy (group 2) groups were 10.8 year (SD ±2.3) and 11 year-old (SD±2.24) respectively. The youngest patient aged 6 year-old and the oldest was 14 year-old in both groups. Overall, 28 (57.1%) children were male, 21 (42.9%) female. In the steroid group male accounted for 15 (60%) children, female 10 (40%), while in immunotherapy group number of male was 13 (54.2%) and female was 11 (45.8%). There were no significant differences between the groups in age and sex distribution.
Table 1. The characteristics of study subjects in steroid and immunotherapy group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (♂: ♀)</td>
<td>Steroid: 15:10</td>
<td>Immunotherapy: 13:11</td>
</tr>
<tr>
<td>Age (x ± SD)</td>
<td>10.8 ± 2.3</td>
<td>11.0 ± 2.24</td>
</tr>
<tr>
<td>Atopy (n [%])</td>
<td>9 (36%)</td>
<td>10 (41.7%)</td>
</tr>
</tbody>
</table>

- Values are significantly different, p<0.05
- Statistic analysis: * Chi-square, ** t test (2 free sample), *** Chi-square

Figure 1. Sex distribution in Group 1

Figure 2. Sex distribution in Group 2

Figure 3. Distribution of age in Group 1

Figure 4. Distribution of age in Group 2
Description of FEV₁ reversibility results

Table 2. The increasing of FEV₁ reversibility of asthmatic patients before and after intervention in each group

<table>
<thead>
<tr>
<th>No</th>
<th>Group</th>
<th>Pre treatment:</th>
<th>Post treatment:</th>
<th>Difference:</th>
<th>p value:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Steroid</td>
<td>21.4±7.3</td>
<td>7.4±4.7</td>
<td>-14 (65.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>2</td>
<td>Immunotherapy</td>
<td>21.3±7.4</td>
<td>7.7±5.0</td>
<td>-13.4 (62.9%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Statistical analysis: paired t test

The increase of FEV₁ reversibility more than 12% is diagnosed as reversible airway obstruction. In this study, the mean of FEV₁ reversibility before intervention in both group increased significantly (x̄ steroid = 21.4 ± 7.3, x̄ immunotherapy = 21.3 ± 7.4). It meant there was a functional hallmark of airway obstruction in all group. In first group, the FEV₁ reversibility decreased as far as 65.4%, while in second group 62.9%. The values of FEV₁ reversibility after intervention significantly differed to the before one from each group (group 1 & 2: p= 0.0001).

Table 3. The comparison of mean values of FEV₁ reversibility before and after intervention among group 1 and group 2

<table>
<thead>
<tr>
<th></th>
<th>Steroid:</th>
<th>Immunotherapy:</th>
<th>p value:</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ reversibility</td>
<td>21.4±7.3</td>
<td>21.3±7.4</td>
<td>0.939</td>
</tr>
<tr>
<td>Pre</td>
<td>7.4±4.7</td>
<td>7.7±5.0</td>
<td>0.872</td>
</tr>
</tbody>
</table>

Statistical analysis: t test

The value of FEV₁ reversibility before intervention among group 1 & 2 was similar (p₁= 0.939, p₂=0.872). It seemed that all of group received the initial therapy with the similar degree of airway obstruction. And after intervention, the decreasing of FEV₁ reversibility of the second group did not differ to the first one.

Table 4. The comparison of “Asthmatic Score” between steroid & immunotherapy group before intervention

<table>
<thead>
<tr>
<th>Pre Treatment</th>
<th>Group:</th>
<th>p value:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid:</td>
<td>Immunotherapy:</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>15(60%)</td>
<td>12(50%)</td>
</tr>
<tr>
<td>Scobe 2</td>
<td>9(36%)</td>
<td>12(50%)</td>
</tr>
<tr>
<td>Segre 3</td>
<td>1(4%)</td>
<td>0(0%)</td>
</tr>
</tbody>
</table>

Statistical analysis: Mann Whitney

There were no significant differences of asthmatic scores that described symptoms of asthma attack between 2 groups before study (p=0.580). In the first group, sixty percent of patients woke up at night at least once because the child had a cough or other asthma symptom, but it released spontaneously without albuterol inhalant. And approximately one third of the patient used inhalant albuterol because of cough or other asthma symptoms for at least once a night. Only one patient that frequently woke at night due to cough or other asthmatic attack. In the second group, 50% had symptom that released spontaneously, and 50% more had to use inhalant albuterol to release the symptom.
Table 5. The comparison of “Asthmatic Score” between steroid & immunotherapy group after intervention

<table>
<thead>
<tr>
<th>Group:</th>
<th>Post Treatment</th>
<th>p value:</th>
<th>STE2oid: n (%)</th>
<th>Immuno therapy: n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0</td>
<td>13(52%)</td>
<td>10(41.7%)</td>
<td>0.571</td>
<td></td>
</tr>
<tr>
<td>Score 1</td>
<td>12(48%)</td>
<td>14(58.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-Statistic analysis: Chi-Square

The asthmatic scores before and after all treatments were analyzed with Wilcoxon Signed Rank Test and revealed that the clinical outcome of Group 1 was similar to Group 2 (p=0.571).

**DISCUSSION**

In this present study, we investigated whether house-dust immunotherapy is effective in asthmatic children with the improvement of asthmatic score and lung function test. And we analyzed and coequalled the value of FEV₁ reversibility before and after inhalant bronchodilator at the initial treatment and 6 months later on steroid and immunotherapy groups. Exactly there was a significantly improvement of FEV₁ reversibility in both groups (p₁=.0001 and p₂=0.0001). And the efficacy of group 2 was as similar as the previous group.

It has published that gender; age, body weight, and height influence the result of lung function test (Frew 2003). So, initially we analyzed that variables in both group, and we concluded that there were no a significant differences. They revealed there were not significant differences.

Lung function testing was performed in accordance with standardized guidelines. Lung function test with spirometer can be done in a cooperative child to establish the diagnosis forcibly, even in mild asthma. Forced Expiratory Volume at one second (FEV₁) is the most sensitive measurement for establishing the diagnosis of asthma. We have to measure FEV₁ before and after inhalant bronchodilator to assess the disease and the improvement as far as 12% or more show a reversible airway obstruction.

Allergen immunotherapy has been demonstrated to inhibit allergic airway inflammation and airway hyper-responsiveness. Recently, Creticos and colleagues demonstrated a reduced seasonal increase in allergen specific immunoglobulin (Ig)E and reduced skin-test sensitivity to allergens during immunotherapy. The specific immunologic mechanisms by which immunotherapy achieves its effect have improved in the last decade. The induction of “blocking antibodies,” down regulation of Th2 lymphocytes and/or up regulation of Th1 lymphocytes, or the induction of CD8 “suppressor” T cells has all been postulated as possible underlying mechanisms (Creticos 1984).

Although acute inflammatory responses in atopic asthma appear fully reversible, repeated episodes induce a chronic state of inflammation; this may lead to the development of irreversible responses, collectively referred to as airway ‘remodeling’. Prominent features of remodeling include sub epithelial fibrosis (excess deposition of collagen in the sub epithelial layer), smooth muscle hypertrophy, and goblet cell hyperplasia. These changes have important functional consequences, including loss of dispensability of asthmatic airways, permanent airflow obstruction, and bronchial hyper reactivity, all of which persist even in the absence of further exposure to antigens. Goblet cell hyperplasia has been shown to be a feature of steroid-resistant asthma, and aspects of the response to steroids may in fact enhance collagen formation. Remodeling of the airway may be an important cause of morbidity in persistent asthma, and currently available therapies are not capable of reversing these changes (Creticos 1984; Durham 1996).

In the present study we examined whether a semi rush immunotherapy protocol according to allergen immunotherapy was effective in this study. It is demonstrated that there was a significant reducing in the airway hyper-responsiveness of all groups. Reducing of airway inflammation characterized by decreasing of FEV₁ reversibility that related to inhibition of eosinophil infiltration to the lung tissue, trachea, and other parts. It coincides with a reduced production of interleukin-4 as the growth factor for eosinophil by antigen-specific T cells in the draining lymph nodes.

The reducing of asthma symptoms (asthma score) related closely to the reducing degree of bronchoconstriction. It can be measured more accurately by lung-function test. The recommendations of the National Asthma Education Program indicate that such testing is essential in the diagnosis and management of asthma because of evidence that both
patients and physicians have inaccurate perceptions of the severity of asthma that contribute to delays in treatment. Indeed, underestimation of the extent of airflow (airway) obstruction is associated with increased mortality in asthma. Physicians cannot identify obstructive or restrictive patterns reliably from history taking and physical examination alone. When physicians ordering lung-function tests were asked to predict the results, they correctly predicted an obstructive pattern 83 percent of the time. However, predictions of normal or restrictive patterns were correct only about half the time. Besides identifying abnormalities, lung function tests allow the severity of an abnormality to be quantified and the presence of reversible airflow obstruction to be determined (Freeman 1994; Gavett 2003).

Forced Expiratory Volume in One Second (FEV₁) is the amount of air that is forcefully exhaled in the first second of the FVC test. In general, it is common in healthy individuals to be able to expel 75% - 80% of their vital capacity in the first second of the FVC test. Hence, FEV₁ is a pulmonary function value that is highly diagnostic of obstructive disease, but FEV₁ alone cannot be used to diagnose obstructive and restrictive disorders all by itself. If the patient demonstrates a reduced FEV₁, the patient may repeat the test after inhaling a bronchodilator. The bronchodilator dilates the bronchial passages and reduces airflow obstruction. The post-bronchodilator test often shows an improved FEV₁ - often times a 10% - 15% improvement. This simple clinical test of FEV₁ reversibility strongly suggests that the FEV₁ was low due to obstructive phenomenon. If the FEV₁ did not change, it suggests the FVC was possibly low due to restrictive pathologies. It is expressed as liters. While FEV₁ reversibility is accounted from:

\[
\text{FEV₁ reversibility} = \frac{\text{FEV₁ after bronchodilator} - \text{FEV₁ before bronchodilator}}{\text{FEV₁}} \times 100\%
\]

It is a sensitive parameter to estimate the extent of airflow obstruction and to monitor the result of therapy. This variable showed a progressive result in both interventions (Brusselle 2004).

We observed that 3 of 24 (12.5%) children in immunotherapy group suffered a mild adverse effect, which was to say local weal-and-flare. But there was not a systemic side effect recorded. Allergen immunotherapy, as well as guidelines, up dates and recommendations of the World Health Organizations is a promising immunomodulation therapy for allergic disease including for allergic asthma in children (Abba 2003).

Specific allergen immunotherapy is an effective treatment of allergic asthma. Advantages of immunotherapy compared with most pharmacotherapies include modification of the natural history of allergic disease, reduction of need for chronic medication, reduction of the clinical symptoms, and improvement of the lung function (McHugh 1995). Finally we conclude that specific immunotherapy with house-dust extract is as effective as inhaled Budesonide in improving lung function test in the term of FEV₁ reversibility in asthmatic children.

REFERENCES


