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Original Article

Low-dose sublingual immunotherapy compared to subcutaneous immunotherapy and conventional therapy in childhood asthma

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ABSTRACT

Background Evidence begin to accumulate that high-dose sublingual immunotherapy (SLIT) is as effective as subcutaneous immunotherapy (SIT) in the treatment of childhood asthma. Since the capacity of sublingual area is similar whether the dose is high or low, the efficacy of low dose may be important to be studied.

Objective To investigate the efficacy of low-dose sublingual immunotherapy in the treatment of childhood asthma.

Methods Parents signed informed consent prior to enrollment, after having received information about the study. Patients were moderate asthma aged 6-14 years with disease onset of less than 2 years before the commencement of the study and peak expiratory flow rate (PEFR) variability of more than 15%. Patients were randomly allocated into group A, B, and C who received subcutaneous immunotherapy, low-dose sublingual immunotherapy, and conventional asthma therapy, respectively. Randomization was stratified into two strata according to age i.e., 6-11 years or 11-14 years. Patients of each stratum were randomized in block of three for each group. At the end of three months, lung function tests were repeated. The primary outcome was PEFR variability at the end of the study. The study was approved by the Ethics Committee of Soetomo Hospital Surabaya.

Results Distribution of variants as represented by sex, age, eosinophil count, and total IgE concentration were normal in the three groups. PEFR variability decreased significantly from 16.97 ± 0.81 to 8.50 ± 5.08 and 17.0 ± 0.87 to 8.40 ± 4.72 in group receiving SIT and SLIT, respectively ($p<0.05$), but decreased not significantly from 17.00 ± 0.83 to $10.82\pm0.5.41$ in control group ($p>0.05$).

Conclusion Low-dose SLIT is as efficacious as SIT in the treatment of moderate asthma in children **[Paediatr Indones 2004;44:243-247].**

Keywords: *childhood asthma, sublingual immunotherapy, subcutaneous immunotherapy, efficacy, moderate asthma*

Immunotherapy is applied to asthmatic patients who are sensitive to inhalant allergen. In patients sensitive to house dust, house dust extract is used accordingly. WHO and various allergy, asthma, and immunology experts throughout the world met in Geneva in January 1997 to make guidelines for allergen immunotherapy. The editor and panel members reached a consensus about the criteria to be included in the WHO position paper of "Allergen immunotherapy as a therapeutic vaccines for allergic diseases".[1] Meta-analysis indicates the efficacy of subcutaneous immunotherapy in the management of asthma.[2] It has been recently proved that sublingual immunotherapy with high dose of house dust extract is as effective as subcutaneous immunotherapy.[3] The safety profile, assessed in clinical trials and post marketing surveillance studies, is satisfactory. Sublingual immunotherapy is now accepted by WHO as a valid alternative to the subcutaneous route, even in children. Although the long lasting efficacy has been recently documented for the sublingual route, several points still need to be elucidated, including optimal dosage.[4]

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We conducted a study to determine whether low-dose sublingual immunotherapy is as effective as subcutaneous immunotherapy or conventional therapy in moderate asthma.

Methods

Patients

Between January and August 2003, we recruited patients aged 6-14 years who had symptoms of moderate asthma with the onset of less than 2 years before the commencement of the study. Moderate asthma was defined by the presence of wheezing, cough, dyspnea, or chest tightening at least once per week but not more than once daily, with reversible airway obstruction defined as PEFR variability of more than 15% between the two highest and two lowest peak expiratory flow rates during 14 days. PEFR variability of >15% without bronchodilator, calculated out of 14 days period after discarding the first three days values, was formulated as:

$$\text{PEFR Variability} = \frac{(A1+A2) - (B1+B2)}{(A1+A2)} X100\%$$

A1 = highest PEFR
A2 = second highest PEFR
B1 = lowest PEFR
B2 = second lowest PEFR

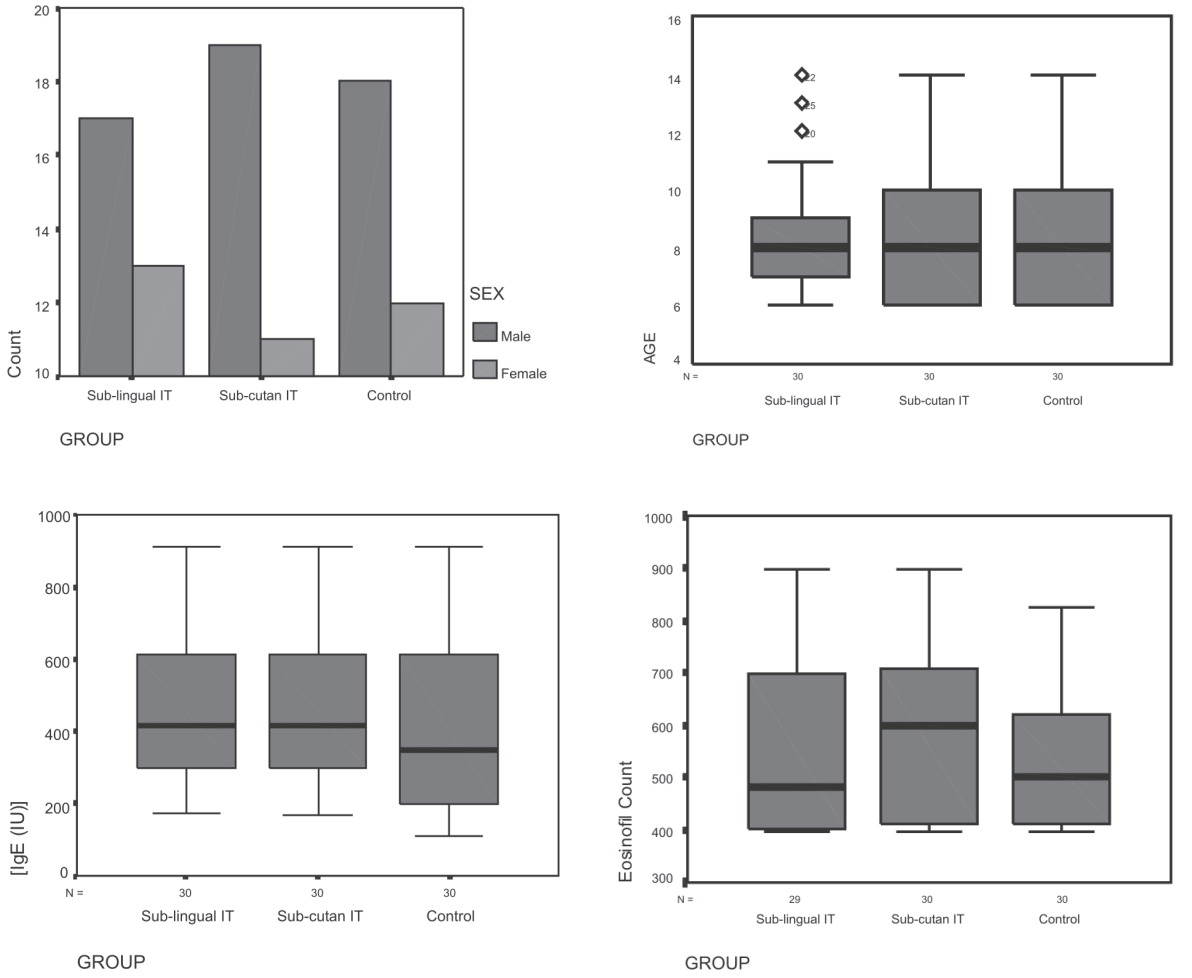

Figure 1. Homogeneity of variants between groups

Exclusion criteria were having asthma symptoms or treatment for more than 2 years before the entry to the study, more than 30 days of treatment with glucocorticoid, more than one depot glucocorticoid injection per year, inappropriate delay of inhaled glucocorticoid treatment, or clinically significant disease. Patients or their parents gave written informed consent.

Study Protocol

Parents signed informed consent prior to enrollment. Patients were randomly allocated into group A receiving subcutaneous immunotherapy and conventional therapy, group B receiving low-dose sublingual immunotherapy and conventional therapy, and group C served as the control group receiving only conventional asthma therapy. Conventional asthma therapy comprising theophylline 3 mg per kilogram body weight and salbutamol 1 mg per kilogram body weight were given to the patients as a rescue treatment whenever asthmatic attack occurred during study. If these drugs failed to overcome the symptom, additional therapy comprising inhaled beta-2 agonist; inhaled, oral, or intramuscular corticosteroid; subcutaneous epinephrine, might be given. If conventional asthma therapy and additional therapy failed to overcome the symptom, the patient was considered as having status asthmaticus and was rejected from the study.

Randomization was stratified into two strata according to age, 6-11years or 11-14 years. Patients of each stratum were randomized in block of three for each group.

Specific subcutaneous immunotherapy was house dust extract with weekly incremental doses of 0.1 ml, 0.15 ml, 0.22 ml, 0.32 ml, 0.48 ml, 0.72 ml, 1 ml of 0.05 mg/ml solution, continued with 0.1 ml, 0.15 ml, 0.22 ml, 0.32 ml, 0.48 ml, 0.72 ml, 1 ml of 0.5 mg/ml solution, continued with maintenance dose of 0.1 ml of 5mg/ml solution in three-week interval. Low-dose sublingual immunotherapy used was Novocare(R) sublingual extract with weekly incremental doses of 2, 4, 6, 8, 10, 12, and 14 drops of first strength solution, continued with 2, 4, 6, 8, 10, 12, and 17 drops of second strength solution, continued with 2 drops of third strength solution with an interval of 3 weeks. At the end of three months, lung function tests were repeated. The primary outcome was PEFR variability at the end of the study. Another outcome assessed was the number of prescription for each patient.

This study was approved by the Ethics Committee of Soetomo Hospital Surabaya.

Sample Size

To meet normal distribution, sample size was determined to be 30 patients in each group. The sample size was calculated based on the formula for difference between proportions for independent groups with a power of 95%.

Statistical Analysis

The Wilcoxon signed rank test was applied to compare the results of PEFR variability at baseline and post treatment. To analyze the data between groups, the Mann-Whitney U test was used. A p level of <0.05 was considered significant.

Results

Distribution of sex, age, eosinophil count, and total IgE concentration in the three groups were comparable (**Figure 1**).

PEFR variability decreased from 16.97 ± 0.81 to 8.50 ± 5.08 in group receiving SIT ($p<0.05$), and from 17.0 ± 0.87 to 8.40 ± 4.72 in group receiving SLIT ($p<0.05$), but decreased not significantly from 17.00 ± 0.83 to 10.82 ± 0.541 in the control group ($p>0.05$) (**Figure 2**).

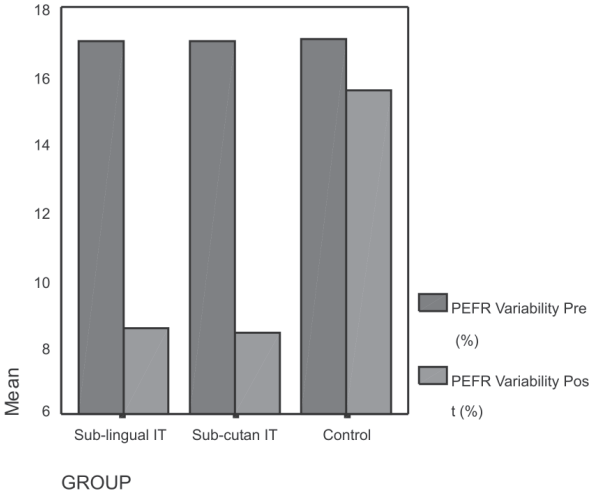

FIGURE 2. PEFR VARIABILITY: PRE AND POST TREATMENT

Group A (SIT) and group B (SLIT) received fewer conventional asthma therapies and received no additional asthma therapy compared to the control group (**Table 1**). The SIT group differed not significantly with the SLIT group ($p>0.05$), while the SIT and SLIT groups differed significantly with the control group ($p<0.05$). No adverse effects were observed in the three groups.

TABLE 1. RESULTS OF PATIENTS' MEDICATION

	Mean number of prescription		
	SIT (Group A)	SLIT (Group B)	Control Group
Conventional asthma Therapy	1+1.1	1+1.7	6+4.3
Additional asthma therapy	-	-	2+1.5

Discussion

This study compared the efficacy of low-dose sublingual immunotherapy versus subcutaneous immunotherapy with house dust extract in children with moderate asthma previously treated with conventional treatment. The control group was children with moderate asthma treated with conventional treatment. The major outcome, indicating the efficacy of treatment, was PEFR variability. The results of this study showed a clinical benefit of sublingual immunotherapy with low-dose allergen in the term of PEFR variability parameter. A significant improvement was also observed in the SIT group compared with the control group.

Low-dose regimens for desensitization have been widely used by mainstream allergists, although their effectiveness is still disputed. In the last few years, there has been a resurgence of interest in the possibility of achieving desensitization by giving topical high-dose allergen. Most studies of SLIT on human were small but show fairly consistent benefits on symptom scores, with few systemic side effects.[5,6]

The theoretical basis for sublingual immunotherapy rests on two concepts. First, it is proposed that allergens given through the mucosal surface are handed differently from those given parenterally, leading to a special immunological tolerance. Second, it is proposed that giving the allergen directly to the target organ may lead to down-regulation of local effectors' responses. Clearly, both mechanisms can happen when the allergen is given directly to the target organ (e.g., nasal immunotherapy), whereas indirect routes, including SLIT, rely on the first of these propositions. From a theoretical point of view, the mucosal surface has to deal with regular exposure to a wide range of innocuous material, and its default response is set to no response.[7] This is in contrast with the internal immune defenses, which are not normally exposed to foreign material because of the barrier epithelial defenses. Anything that reaches the internal defenses must have breached the external barriers and can therefore be considered dangerous, whereas most material seen at the surface may not be going anywhere and can be ignored.

The more complex questions arise regarding why some foreign materials will elicit an immune response at the mucosal surface, despite being incapable of invasion, and furthermore why some materials elicit allergic-type responses while others drive more conservative IgG responses. This issue lies at the heart of what makes an allergen allergenic and also determines whether we may be able to achieve desensitization by means of topical route. Experimental support for this theory is available. It has been shown that locally administered allergen is taken up by mucosal dendrite cells, and at least in nonsensitized mice, the allergen is then presented to T cells together with Il-12, thereby biasing the response toward a Th1 profile and away from the pro-IgE Th2 profile.[8] It is unclear whether this mechanism can suppress established allergic responses, which is the situation that we would wish to achieve with SLIT. It is clear, however, when allergen is given by the sublingual route to allergic human subjects, the allergen is retained in the buccal region much longer than if the allergen is simply placed in the mouth and then swallowed, suggesting that allergens are indeed taken up locally after sublingual administration.[9]

In contrast to animal models, the immunologic response to SLIT in human studies has been relatively modest. Some changes have been found in skin sensitivity, but most studies have not found any change in systemic parameters, such as specific IgE, specific IgG, or T cell-cytokine balance.[10] A study using *Parietaria judaica* allergen administered

sublingually in patients with allergic *rhinoconjunctivitis* showed a significant increase in specific IgG_4 in the treatment group.[11]

Giving the allergen by mouth rather than by injection can increase compliance of the patients to follow the treatment procedure. It also decreases the cost of SIT by reducing the need for medical and nursing time, as well as cost of consumables, such as syringes and needles.

In conclusion low-dose SLIT is as efficacious as SIT in the treatment of moderate asthma in children.

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