Use of Superoxide Dismutase in Accelerating Symptom Relief in Asthmatic and House Dust Mite Allergic Children Receiving House Dust Mite Immunotherapy

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Abstract

Objective: To evaluate the efficacy of superoxide dismutase (SOD) in lung function (FEV1 reversibility) and respiratory symptoms (drug scores, symptoms scores) in asthmatic and house dust mite allergic children receiving house dust mites immunotherapy.

Methods: Forty subjects aged 6–17 years old with asthma, tested positive for house dust mite allergy on skin prick test, and received immunotherapy were enrolled in this study. All subjects completed clinical based assessments and diary-based assessments for drug and symptom scores. Following a four-week baseline assessment, all subjects were randomized to receive SOD or placebo. Respiratory symptoms (drug and symptoms score) and FEV1 were evaluated at the end of the 1st, 2nd, 3rd, and 4th weeks after randomization. Drug score, symptoms score, and FEV1 reversibility test results were analyzed using a Paired t test and repeated measure of ANOVA.

Results: There was a significant difference in drug scores, symptoms score, and FEV1 reversibility test outcomes between SOD and placebo. SOD group showed a significant decrease in all outcome measures compared to those in placebo group.

Conclusions: The use of SOD as antioxidants is effective in accelerating symptom relief for children with asthma and house dust mite allergy receiving house dust mite immunotherapy.

Received:
May 6, 2015

Revised:
August 9, 2015

Accepted:
August 28, 2015

Keywords: Allergic asthma, antioxidant, drug score, immunotherapy, symptoms score

IJIHS. 2015;3(2):72–8

Introduction

Asthma is one of the common health problems in almost all countries in the world. Asthma prevalence appears to have peaked or reached a plateau in countries with a high prevalence, while it is still rising in many Asian cities.[1] In Indonesia, the prevalence of allergic asthma in school aged children is 2.1%.[2] The prevalence is increasing each year and reached 6.9% in 2008.[3] Secondary prevention of asthma allergy through house dust mite (HDM) immunotherapy has been shown to improve the natural course of allergic disease. Immunotherapy is more effective against aeroallergen. The benefits gained in a minimum of 14 weeks; however, dropping out is still inevitable.[4] In the outpatient allergy clinic of Dr. Soetomo Hospital, 19.8% patients dropped out of the scheduled immunotherapy program in 2006 and 25.3% in 2007.[5] To accelerate the benefit (symptom relief), other therapies should be considered to compliment the desired outcomes.

Antioxidant use has been proposed as an adjuvant therapy in allergic asthma children treated with house dust mite immunotherapy.[6,7] Superoxide dismutase (SOD) is an antioxidant that reduces inflammation caused by oxidative stress or further structural cell damage through oxidation of proteins, fats and DNA.[6,8] Antioxidant or immunomodulator

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given concurrently with house dust mite immunotherapy as a complementary and alternative medication has not yet been well-acknowledged. This study examined the clinical efficacy of SOD in accelerating symptom relief in children with allergic asthma and house dust mite allergy receiving house dust mite immunotherapy in a double blind randomized controlled clinical trial.

Methods

The interventional study was a randomized double-blinded, placebo-controlled design. The study took place from October 2013 to April 2014. Subjects received oral SOD or placebo once daily for a period of 4 weeks. The protocols of subject selection were followed and immunotherapy commenced as in the hospital guidelines. The study included a nurse to witness the administration of 250 mg oral SOD-gliadin and saccharum lactis-consisted placebo as the control group, while parents of the subjects were instructed to continue giving the supplementation as per advise.

Data collection includes several clinical assessments, lung function (FEV1 reversibility) and respiratory symptoms (drug scores, symptoms scores) at the randomization period and at 1st, 2nd, 3rd, and 4th week following randomization. Supplementation is given for 4 weeks. Subjects completed diaries in the first and third weeks of run in (two diaries of seven days) and in the first and every other week (five diaries of seven days) after randomization.

Subsequently, the subjects were randomly assigned into 2 groups. For allocation of the subjects, a computer-generated list of random numbers was used. One group was given SOD-gliadin combination of 250 mg and the other group a placebo. Each supplement was given once daily for 4 weeks. During the intervention period, measures taken for FEV1 reversibility once a week and all subjects were to complete a written-diary recording asthma symptom scores, asthma drug scores, questions on tolerance and acceptance of the product, and gastrointestinal complaints.

Concurrent medication for all disorders, including asthma, was not changed. Subjects with moderate or severe persistent asthma attack or with a history of respiratory failure were excluded. Other exclusion criteria were smoking, history of oral steroid intake, rectal, or parenteral within 28 days prior to first visit or at any time during the study. In addition, subjects suffering from mental retardation, congenital heart disease, malignancies or having poor nutritional status were also excluded. Consecutive sampling was done and written informed consent was taken. Ethical approval was obtained from Dr. Soetomo General Hospital Research Ethics Committee.

Subjects with asthma were obtained from the Allergy Outpatient Clinics of Dr. Soetomo General Hospital. Over 100 subjects were sensitized to house dust mite, as determined by skin prick test, and receiving house dust mite immunotherapy. We included only those subjects with a positive result to house dust mite (wheal diameter 3 mm greater than

Table 1 Baseline Values Before Randomization Period for All Subjects

Variable	Supplement Group		p Value
	SOD (n=20)	Placebo (n=20)	
Age, mean (SD) yrs.	9.55 (2.19)	9.00 (1.49)	0.385
sex, n			
male	10	13	0.990
Female	10	7	
Body weight, mean (SD) kg	31.00 (11.52)	26.55 (7.97)	0.163
Body height , mean (SD) cm	133.40 (13.47)	131.35 (12.01)	0.286
$FEV_{1\ reversibility}$*pre*, mean (SD)	23.52 (14.65)	23.22 (11.64)	0.944
Medication (asthma drug) scores	7.05 (6.78)	7.75 (6.97)	0.749
Symptom scores	11.65 (11.98)	13.85 (10.49)	0.540

Clinical efficacy of SOD

control) and greater than other aeroallergen extracts result. Eligible subjects with consent were enrolled into the baseline recording period. Forty subjects aged 6–17 years old with intermittent to mild persistent asthma, according to GINA 2006 criteria, were included.[9] Diagnosis of asthma were determined by the level of FEV1 reversibility ≥12% normal value, measure at 15–30 minutes after administration of inhaled salbutamol during the 1st visit.

During the clinical trials, the variability in asthma symptoms such as improvement and deterioration were considered important to be observed. Subjects were excluded from clinical trials when there was an evidence of a decreasing quality of life according to their diaries, or if subjects failed to complete the diary for at least ten days during the study.

Subjects will be excluded when subjects were known to participate in other clinical trial for other drugs in the previous 30 days, recent administration of SOD, pregnant, lactating, suffering from respiratory tract infections in the past three weeks, or change the asthma medication that has been programmed in the two weeks prior to clinical trial.

Several independent pharmacists in the Pharmaceutical Unit Dr. Soetomo General Hospital prepared 250 mg of SOD-gliadin and saccharum lactis-consisted placebo. The placebo was matched to the study drug for taste, color, and size. Drugs were stored in a secured area in accordance with the standard operating procedures of good clinical practice. The individual treatment drugs were decoded as A or B by independent researchers who were blinded to the designated drugs given. The first 10 subjects were randomized using a sealed envelope. All subsequent subjects were allocated to A or B by a process of minimization according to age, sex, and severity of asthma assessed on the diaries.[10] The subjects and research nurses recorded whether treatment A or B had been given the day after dosing. The randomization codes were revealed when the study had been completed.

Measures taken were recorded in the clinic and on diary cards. At baseline, results FEV1 reversibility, the subject's attitude to other medicine, and the results of routine blood screening for undetected systemic illness were

Table 2 Variables Measured at Clinic Visits (FEV1 Reversibility) and from Diaries (Drug Score and Symptoms Score) at the Randomization Period (Week 0) and at 1st, 2nd, 3rd, and 4th Week after Randomization

Outcomes Variables and Treatment Group	Time of Assessment for Outcome Variables					p Value
	Week 0	Week 1	Week 2	Week 3	Week 4	
$FEV_{1\ reversibility}$, mean (SD)						
SOD Group	23.52 (14.65)	9.57 (6.73)	9.85 (6.74)	6.95 (5.51)	7.49 (7.36)	0.000*)
Placebo Group	23.22 (11.64)	18.94 (11.06)	22.75 (23.10)	18.48 (10.32)	21.25 (18.34)	0.000*)
P	0.944**)	0.002**)	0.022**)	0.000**)	0.003**)	0.020***)
Medication scores(SD)						
SOD Group	7.05 (6.78)	1.50 (2.40)	1.00 (2.00)	0.40 (1.10)	0.25 (1.12)	0.000*)
Placebo Group	7.75 (6.97)	8.30 (7.53)	7.20 (7.47)	4.80 (5.21)	5.60 (5.47)	0.000
P	0.749**)	0.000**)	0.001**)	0.001**)	0.000**)	0.009***)
Symptom scores (SD)						
SOD Group	11.65 (11.98)	3.30 (3.25)	3.00 (5.65)	2.30 (2.76)	3.05 (4.08)	0.000*)
Placebo Group	13.85 (10.49)	13.05 (7.91)	14.85 (12.05)	11.05 (6.44)	8.60 (5.28)	0.000*)
P	0.540**)	0.000**)	0.000**)	0.000**)	0.001**)	0.005***)

*): differences between the group treatments for outcome variables
**): differences between the week of assessment for outcome variables
***): interactions between the group treatments and week of assessment for outcome variables

recorded. Blinding method was confirmed one day after randomization, when subjects and investigators were asked separately to determined subjects given 250 mg of oral SOD-gliadin or placebo.

At randomization, FEV1 were recorded as the maximum of three blows. The predicted FEV1 was calculated using the formula. Drug and symptoms scores were recorded on diary. Mean scores were calculated for the run-in period and for each of the five weeks of the assessment after randomization. Subjects were assessed on the symptoms at night, first thing in the morning, and during the day. The frequency of symptoms and the drug consumed were calculated for each assessment period. Subjects used inhaled bronchodilator as required. Bronchodilator consumption was assessed by the frequency of daily use of the prescribed bronchodilator during each of the assessment periods.

An initial sample size of 40, with a 0% drop out rate (giving a final number of 40), would give a power of 80% for detecting a 30% difference in proportion of subjects who receive house dust mite immunotherapy cured by SOD compared to placebo, based on the cure rate of allergic children who received immunotherapy with SOD by 60% on our previous research and a two tailed test at the 5% level.

FEV1 and quality of life from diaries, in the form of drug and symptom scores, were the outcome variables. The primary endpoint was the proportion of subjects achieving an improvement in FEV1 reversibility from baseline to 4 weeks. All outcome measures such as lung function (FEV1 reversibility) and respiratory symptoms (drug scores, symptoms scores) were examined for suitability of parametric analysis. Clinical efficacy tested by comparing the two treatment groups (at the randomization period and at 1st, 2nd, 3rd, and 4th week after randomization). Asthma symptom scores, asthma drug scores, and FEV1 reversibility test results were analyzed using a paired t test and repeated measure of ANOVA. Outcome assessors and data analysts were kept blinded to the allocation. The analysis was involved all subjects who were randomly assigned.

Results

Baseline data were recorded from fourty asthmatic children allergic to house dust mite who received house dust mite immunotherapy. Forty subjects were given 250 mg oral SOD-gliadin and saccharum lactis-consisted placebo as control, and all fourty subjected completed all clinical assessments. No subject reported adverse drug reaction due to 250 mg of oral SOD-gliadin along the course of study. Baseline details of the two groups were similar (Table 1).

There was a significant increase of FEV1 reversibility in both groups and significant improvements were shown in symptom score, while drug score showed a significant decrease for both groups. There was a significant difference between the groups in terms of all outcome variables (Table 2).

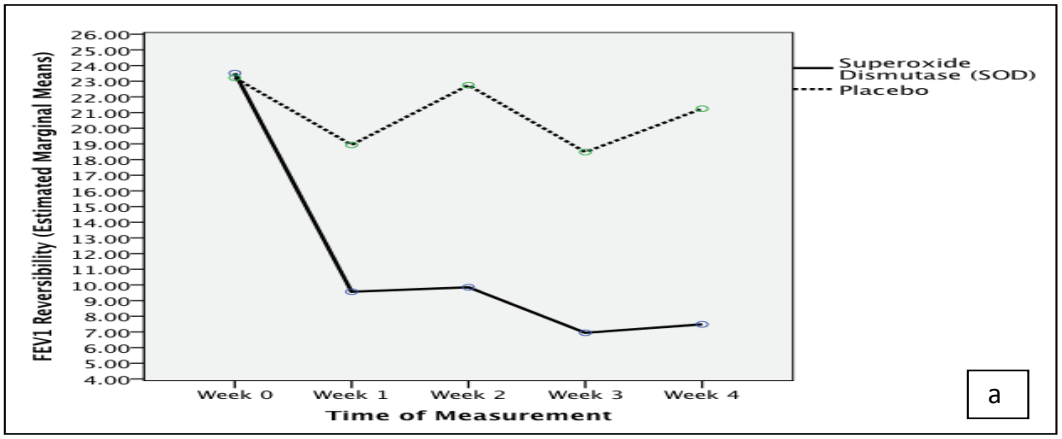
Mean improvement in FEV1 reversibility compared to the baseline value was 1.97% for placebo and 16.03% for SOD-gliadin group, with a mean difference of -9.46 (95% confidence interval for difference -14.02 to -4.89). Mean improvement in medication (drug) scores from baseline was 2.15 for placebo and 6.80 for SOD with mean difference was -4.69 (95% confidence interval for difference -7.12 to -2.26).

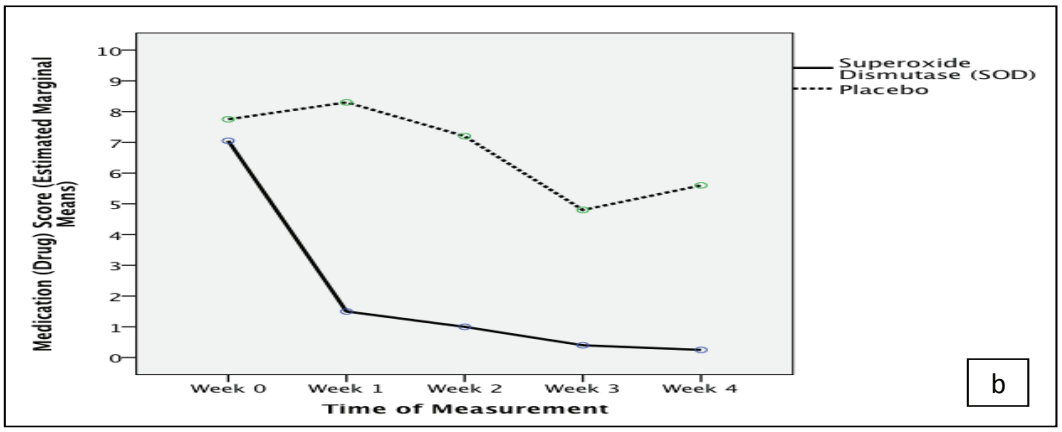
Mean improvement in symptom scores compared to the baseline value was 5.25 for placebo and 8.60 for SOD-gliadin group with a mean difference of -7.62 (95% confidence interval for difference -11.12 to -4.124) (Fig.1).

Significant interaction was found between treatment and week of assessment for FEV1 reversibility (P=0.020), asthma symptom scores (P=0.009), and asthma drug scores (P=0.005), indicating differences between the two therapy groups over the course of the study (Table 2). There was no evidence of significant change in bronchodilator use in either group, although participants in the SOD group were using less bronchodilator than the placebo group in the last four weeks of the study. There was evidence that SOD may accelerate relief of symptoms in asthmatic children allergic to house dust mite who received house dust mite immunotherapy.

Discussion

This randomized double-blinded placebo controlled trial showed that SOD was better than placebo in terms of assisting relief of symptoms in asthmatic children allergic to house dust mite receiving house dust mite immunotherapy. A study stated that the disruption of SOD activity has an important role on the pathophysiology of airway remodeling hyperactivity and subsequently





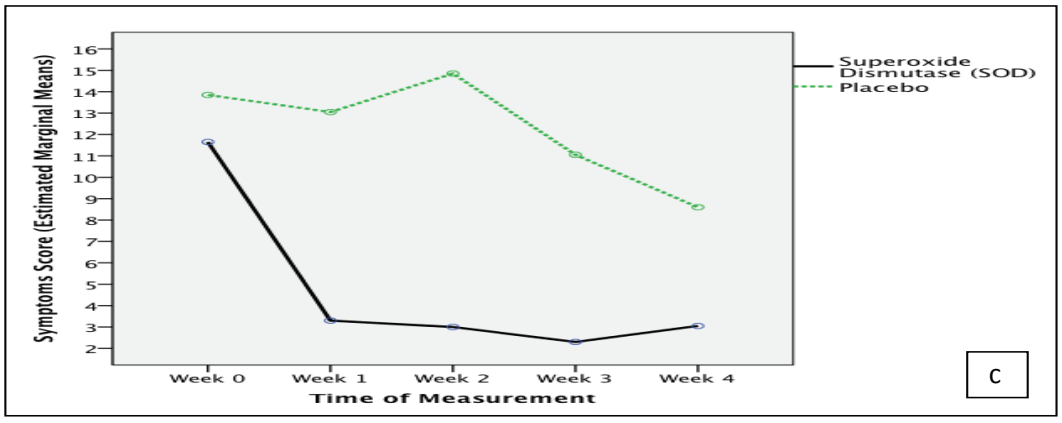


Fig. 1 Variables Measured at Clinic Visits [FEV_1 Reversibility (Fig. 1a)] and from Diaries [Drug Score (Fig. 1b)] and Symptoms Score (Fig. 1c)]) at the Randomization Period (Week 0) and at 1st, 2nd, 3rd, and 4th Week after Randomization

induce apoptosis and cell shedding of airway epithelial cells.[11] Another study also stated that SOD activity in asthma groups was statistically significant (p=0.001) compared to the healthy group.[12] SOD activity was significantly related to airflow limitation which reflected in % FEV1, FEV1/FVC and FEV1 reversibility. Asthma group with low serum levels of SOD showed %FEV1 of ≤80%, whereas in the control group with higher serum levels of SOD showed %FEV1 of >80%. Other than that, SOD activity was inversely related to airway hyperactivity determined by FEV1reversibility measured after ß2-agonist administration. This study supports previous research by Sackesen *et al*.[13] which presented a significantly lower levels of the superoxide dismutase in children with asthma compared to healthy controls.

Several previous studies have shown clinical effectiveness of SOD in asthma. Kumar and Shanmugasundaram[14] conducted a study of 60 children aged 5–18 years old. The sample was divided into 2 groups: the group with asthma and healthy children as control group. All the samples are given antioxidant supplements 250 mg Amrita Bindu twice daily for 12 months. The results showed an increase in serum SOD levels and peak expiratory flow rate (PER) in the asthma group was almost similar to the control group. This study showed a significant improvement of FEV1 reversibility in relation to the antioxidant and anti-inflammatory effect of SOD. Similar finding was shown by Chang and Crapo[15] who reported AEOL 10113 (antioxidant mimetic) reduces the degree of airway inflammation, demonstrated by the decrease in cell numbers of eosinophils, neutrophils and lymphocytes in bronchoalveolar lavage fluid (BALF).

This research has yielded new findings of SOD in the weekly improvement of FEV1 reversibility and in a faster time period when compared to placebo administration in children aged 6–17 years old with allergic asthma who received house dust mite immunotherapy. On the basis of these findings, SOD can be used as adjuvant therapy to improve the benefit of house dust mite immunotherapy, by accelerating the onset of therapeutic effect; hence, the drop out rate can be reduced. This research informs that SOD can be used to improve adherence with the immunotherapy program, because multi-year immunotherapy regimen has been shown problematic, only about 16% adherences at year 3.[16,17] In conclusion, SOD accelerates the symptom relief in asthmatic children allergic to house dust mite receving house dust mite immunotherapy.

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