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Vitamin E Supplementation, Lung Functions and Clinical Manifestations in Children with Moderate Asthma: A Randomized Double Blind Placebo- Controlled Trial

Javad Ghaffari[1], Reza Farid Hossaini[2], Alireza Khalilian[3], Negin Nahanmoghadam[4], Ebrahim Salehifar[5], and Houshang Rafatpanah[6]

[1] *Department of Allergy and Clinical Immunology, Molecular and Cellular Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran*
[2] *Department of Allergy and Clinical Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3] *Department of Biostatistics, Faculty of Health, Mazandaran University of Medical Sciences, Sari, Iran*
[4] *Department of General Pediatrics, Mazandaran University of Medical Sciences, Sari, Iran*
[5] *Department of Pharmacology, Mazandaran University of Medical Sciences, Sari, Iran*
[6] *Department of Immunology, Mashhad University of Medical Sciences, Mashhad, Iran*

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ABSTRACT

Asthma is the most common chronic inflammatory disorder characterized by cough, wheezing and dyspnea in children. Nutrition is an important factor which influences on induction and exacerbation of asthma. There are controversies to use Vitamin E in asthmatic patients. The aim of this study was to evaluate the effect of vitamin E supplement in children with moderate asthma.

This is a randomized double blind placebo-controlled trial performed on children (age 2-17 years old) with moderate asthma (5-17 years old) from March 2010 to March 2012. Case group were treated with fluticasone and vitamin E (50mg/day) and control group received fluticasone plus placebo for 8 weeks.

Out of 300 cases, 240 cases completed the study. Female to male ratio was 0.84. Serum level of Vitamin E significantly increased after treatment in intervention group. FEV1 and FEV1/FVC ratio was significantly improved in case group compared to the control group.

It can be concluded that vitamin E supplement could improve clinical manifestations and pulmonary function test in children with moderate asthma.

Keywords: Asthma; Child; Dietory supplements; Respiratory function tests; Vitamins; Vitamin E

Corresponding Author: Javad Ghaffari, MD; Department of Pediatric Immunology and Allergy, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari, Iran.Tel: (+98 151) 223 3011-15, Fax: (+98 151) 2234 506, E-mail: javadneg@yahoo.com

INTRODUCTION

Asthma is the most common chronic inflammatory disorder with an unknown etiology associated

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with increased reactive oxygen species (ROS) and characterized by cough, wheezing and dyspnea in children.[1-3] The prevalence of allergic disorders such as asthma increased in the several past decades. Prevalence of ever asthma in the north of Iran and a meta-analysis in Iran were 12% and 7.6%, respectively[4,5] Some hypotheses for increasing of asthma are decreased intake of antioxidant diets such as green vegetables and whole grains enriched with vitamin E (fat soluble) and increased consumption of oxidant's diet contained free radicals.[6] Exact etiology of asthma is not clear. Genetic and environmental factors have role in asthma pathogenesis. Nutrition is an important factor in induction and exacerbation of asthma. Modern, urbanized diets (Increased consumption of processed and synthetic foods) and fewer intakes of natural and healthy foods such as vegetables and fruits may contribute to allergic disorders (i.e. Asthma). Researchers are more interested to use antioxidants agents such as Vitamins A, C, D, and E to improve clinical and pulmonary function in asthmatic patients. These agents can decrease or prevent oxidant toxicity on respiratory systems.[7-9] Some reports showed that vitamin E deficiency has been associated with decreased pulmonary Function Test (PFT) and increased asthma manifestations. Inversely, vitamin E supplements both in the form of enriched foods or oral preparations improved clinical manifestations and PFT in asthmatic patients.[2,3] Vitamin E as a fat-soluble agent has important effects on immune system. This agent improves T-cell and granulocyte function. Also, vitamin E contains Tocoferol and Tocotrinol (each has 4 isomers; alpha, beta, gamma and delta) that prevent oxidation of metabolic agents such as unsaturated fatty acids.[10] However; there is a serious concern about anti-asthmatic synthetic drug especially inhaled corticosteroids (ICS). Additive complementary medicine such as vitamin E can decrease ICS dose and therefore, results in lower side effects. Most of human studies conducted in this regard were performed on adult population and there are a few researches in childhood population especially clinical trial studies. The aim of this study was to evaluate the effect of vitamin E on PFT and clinical manifestations in children with moderate asthma.

MATERIAL AND METHODS

This is a randomized double blind placebo-controlled trial that was performed on children with moderate asthma referred to university`s allergic clinic at Bouali Hospital in Sari (Iran) from March 2010 to March 2012. Sample size included 300 cases (each group 150) by following formula based on power 80% and accuracy 95%.

Inclusion criteria were age between 5 to 17 years old, moderate asthma for at least 2 years, FEV1 =60-80%.

Exclusion criteria were abnormal chest x-ray such as pneumonia, mass or infiltration except for hyper aeration, cardiac disease, acute sinusitis in 3 months prior to study, poor cooperation, liver, kidney and other systemic disorders; taking a supplemental nutrition such as vitamins and mineral trace elements, malignancies, gastro esophageal reflux, chest wall deformity.

Diagnosis of asthma was based on clinical manifestations, physical examination and PFT. Because asthma is a clinical diagnosis, the main course of diagnosis of moderate asthma was based on clinical manifestations but spirometry was an additional and support devices. PFT was done for all the patients before and after 8 weeks of treatment (table 3) in afternoon between 16 to 18 o'clock.

The patients were divided into two intervention and control groups: the intervention group took moderate-dose of inhaler steroids (Fluticasone, GSK) and vitamin E (50 mg/day) for 8 weeks; the second group received moderate inhaler steroid (Fluticasone, GSK) and placebo (gelatin, pharmacy faculty, Sari, Iran) for 8 weeks. vitamin E was used in a dose of 50 mg/day.[7]

Serum IgE concentration was determined by enzyme linked immunosorbent assay (ELISA) (Mono bind, USA) according to manufacturer's protocol (IU/ml). All samples were analyzed in duplicate.

We evaluated Vitamin E serum level by chromatography by HPLC system (model: YL9100 HPLC, Young Lin Instruments Co. Ltd, Anyang, South Korea). Serum normal value of vitamin E was 6-10 µg/dl. We considered deficiency of vitamin E under 6µg/dl in children.

Our data was analyzed by SPSS -13 and student t-test. *P*-value less than 0.05 with CI 95% was considered significant. This study was approved by the local scientific and ethic committees of Mazandaran University of Medical Sciences.

RESULTS

Three hundred patients were enrolled in this study from March 2010 to March 2012 (Figure 1). Out of 240 cases in this study, 46% (n=110) were female with mean age of 8.9±2.14 years (case group=8.4±0.9, control group=9.1±1.3); *p*=0.67 (Table 1).

Serum level of vitamin E before treatment was 4.1±1.41 µgr/dl and 4.5±1.8 µgr/dl in case and control groups, respectively. Vitamin E level after treatment was 8.2±2.4 µgr/dl and 4.7±0.9 µgr/dl in case and control groups, respectively (*p*=0.012) (Table 2).

Mean serum IgE level was 154.5±33.8 IU/ml and 118.3±14.4 IU/ml before and after 8 weeks of treatment in cases group (*p*=0.06) but it was 147.2±27.6 IU/ml and 127±22.3 IU/ml before and after 8 weeks of treatment in control group (*p*=0.16).

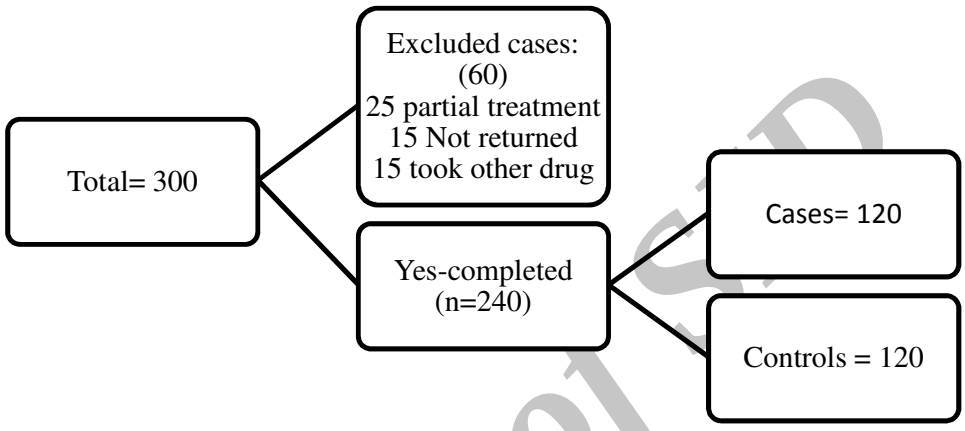

Figure 1. Patient's selection method from March 2010 to March 2012.

Table 1. Demographics characteristics of the case and control groups

Gender/group	Case group (%)	Control group (%)	*P*-value	Total
Male	64(53)	66(55)	0.54	130
Female	56(47)	54(45)	0.52	110
Total	120(100)	120(100)		240
Mean age (years)	8.4±0.9	9.1±1.3	0.67	8.75±1.1

Table 2. Mean serum level of vitamin E in case and control groups in moderate asthmatic children

Vitamin E (mean)	Cases group	Control group
Before Treatment	4.1±1.41 µgr/dl	4.5±1.8µgr/dl
After Treatment	8.2±2.4 µgr/dl	4.7±0.9 µgr/dl
P-value	0.012	0.068

Table 3. Pulmonary function test in case and control groups in moderate asthmatic children

PFT	Case group		*P*-value	Control group		*P*-value
	Before	After		Before	After	
FEV1	71.6±4.1	83.1±5.4	0.001	72.4±3.4	74.8±2.7	0.568
FVC	95.3±2.4	100.2±1.14	0.432	96.1±1.7	95.8±1.6	0.428
FEV1/FVC	74.4±2.1	83.2±9.8	0.032	75.1±1.97	5.5±1.8	0.537

T=treatment; FEV1=forced expiratory volume in 1th time; FVC=forced vital capacity; PFT=pulmonary function test

Table 4. Coughing, wheezing and exercise induced dyspnea in case and control groups in moderate asthmatic children.

Symptom	Cases group (%)		*P*-value	Control group (%)		*P*-value
	Before	After		Before	After	
Cough	83.5	60	0.02	88.4	75.3	0.05
Wheezing	72.7	55	0.03	75.8	68.7	0.14
Dyspnea	32.6	20.4	0.04	37.8	31.4	0.24

The results of PFT in cases and control groups in moderate asthmatic children are shown in Table 3.

We evaluated clinical manifestations in patients before and after 8 weeks of treatment (Table 4).

Statistical Analysis

We recorded all of our data in spss13. Data were expressed as mean ± SD. The comparison between two groups was performed with one way analysis of variance (ANOVA). Correlation was assessed by Pearson correlation (r). *P*-value of less than 0.05 was considered statistically significant.

DISCUSSION

The epithelium lining fluid of lung contains high concentration of antioxidants which has protective effect against inhaled and endogenous oxidants. The main result of this study is that the vitamin E supplement has positive effects on both clinical manifestations and PFT in children with moderate asthma associated with vitamin E deficiency. Similar to our study, Romieu et al. found improvement of PFT (FEV1, FEF_{25-75} and PEF) in children with asthma and prevention against high levels of Ozoneby using a combination of 50mg/day vitamin E and 250mg/day Vitamin C.[7] Vitamin C could improve function of Vitamin E. Contrary to our study, a meta-analysis by Gao J et al showed that antioxidant agents such as Vitamin C and Vitamin E did not reduce prevalence of asthma.[8] Pearson in adult asthmatic patients found no effect of Vitamin E on clinical manifestations and PFT.[9] There are some difference in this study including the dose of Vitamin E used in mild to moderate asthma.

It has been shown by Devereux et al that Vitamin E can have a primary preventive effect on asthma and antenatal vitamin E supplementation was negatively associated with asthma ever and current asthma and cough at 5 years old. Therefore, low maternal intake of vitamin E during pregnancy could increase likelihood of asthma in children.[10] Contrary to the mentioned results, West et al study demonstrated that there was no correlation between prenatal diets enriched with β-carotene, vitamin E or zinc and allergic disorders in one-year-old infants, but vitamin C was associated with low incidence of allergic diseases.[11] Vitamin E deficiency can predispose to asthma and there is a direct correlation between low levels of Vitamin E and inflammatory disorders such as asthma. Similarly, our study confirmed the relation between Vitamin E deficiencies and induction of the asthma. Also, similar results were observed in Scottish cohort study that cough and wheezing were reduced in children (at the age of 2) when their mothers were supplemented with an adequate dose of Vitamin E in pregnancy due to decreased mononuclear proliferative response to aeroallergens.[12,13] Combinational antioxidant therapy (vitamin C with vitamin E or selenium with vitamin E) has been shown to be effective in improving of clinical symptoms and PFT in asthmatic patients.[7] In Martindale's study, Vitamin E and Selenium could significantly improve PFT in children with asthma.[14] Selenium is a trace element that improves clinical manifestations with anti-inflammatory effects. Vitamin E associated with Selenium can act synergistically with anti-inflammatory effects in asthmatic patients.

Some studies showed significant decreases of Vitamin E concentration in asthmatics compared to non-asthmatic patients.[15] Also Al-abdulla showed the mean serum level of Vitamin E was significantly lower in all asthmatic patients with or without attacks compared with non-asthmatic patients. There was direct relation between decrease of mean serum level of Vitamin E and severity of asthma. [16]

Fogarty et al. found that high intake of Vitamin E was associated with lower allergen sensitization and decreased serum IgE level. Therefore, vitamin E could be a preventive factor of allergic disorders.[17] Gilliland found that FEF 25-75 (measure of small airways) was the only pulmonary function parameter that was

decreased significantly after consumption of Vitamin E in boys with asthma. They concluded that vitamin E could protect small airways. In addition, they found decreased in FVC,FEV1 and FEF23-75% with low intake of vitamins A,C and E. [18] In our study, FVC, FEV1 and FEV1/FVC improved significantly by Vitamin E supllementation and this showed the effect of Vitamin E on non-small airways.

Some studies have shown the lack of association between serum concentrations of Vitamin E and prevention of asthma. [19,20]

In a study by Schock et al, it was found that bronchoalevolar Vitamin E (alpha-Tocopherol) level was significantly decreased in atopic patients compared to normal individuals.[21]

Similar to our study, in other researches conducted by Schock et al., pulmonary function levels were lower in children with inadequate intake of antioxidant vitamins. Alpha-tocopherol was decreased in BAL after exercise in mild asthmatic patients but there was no significant difference between stable atopic asthma and the control group.[22]

These differences in serum or BAL concentration of vitamin E were related to diet, severity of disease and analytical technics employed. Further researches showed decrease of antioxidants such as vitamin E in asthmatic patients and a direct relationship between severity of asthma and decreased serum level of vitamin E has been shown.[23,24]

However, irrespective of vitamin E level in lung fluid, it seems that increasing serum level of vitamin E in improvement of asthma manifestations is important and effective.

Allergic disorders such as asthma are sometimes associated with increases in total and specific serum IgE levels and decreasing serum total or specific IgE can improve clinical manifestations of allergic diseases.[17] In our study, significant decrease in serum IgE level was observed after intake of vitamin E supplements and this was associated with clinical and pulmonary function improvement possibly by T-helper cytokine release regulation. [25]

Limitations of this study included short course of therapy, inclusion of only persons with moderate asthma severity and unknown diet regimes of the study group. Also we could not measure the steroid level and serum vitamin C levels that might influence vitamin E effect.

In conclusion, we found that in children with moderate asthma associated with Vitamin E deficiency, 50 mg/day Vitamin E supplement has significant effect on improving clinical manifestations and PFT. So we suggest a study with more sample size with different dosages and longer duration of therapy and/or a study including different groups of patients with different severity of asthma considering their diet and checking their steroid levels.

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