Original Article

Effect of vitamin D_3 on mild to moderate persistent asthmatic patients: A randomized controlled pilot study

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Abstract

Background: Asthma is a common chronic inflammatory disease of the bronchial airways. Well defined treatment options for asthma are very few. The role of vitamin D_3 on asthma is still baffling. Aim: We have examined the effect of vitamin D_3 supplementation in mild to moderate persistent asthma patients. **Materials and Methods:** We conducted an open labeled, randomized comparative trial in 48 asthma patients. The study duration was about 90 days. The study had a run-in-period of 2 weeks. At the end of run-in-period, patients were divided into two groups: Usual care group ($n = 31$) patients received budesonide and formoterol and intervention care group ($n = 32$) patients received vitamin D_3 supplementation along with their regular medicine. **Results:** The primary outcome of the study was to measure the improvement in forced expiratory volume in 1 second (FEV_1). Patients in both groups had a significant improvement in FEV_1 at the end of the study. The mean difference in percentage predicted FEV_1 in usual care and intervention care group was 4.95 and 7.07 respectively. **Conclusion:** The study concluded that adjunctive therapy of vitamin D_3 is effective in asthma patients. The present study will be an evidence based report; however, future studies are warranted in longer duration of time to substantiate the present findings.

Key words: Asthma, budesonide, forced expiratory volume in 1 s, formoterol, vitamin D_3

INTRODUCTION

Asthma is a common chronic lung disease affecting 300 million people and its prevalence increases globally by 50% every decade.[1] In recent days, there are more numbers of reports of the association between vitamin D deficiency and a widespread range of conditions such as cancer, depression, cardiovascular diseases, diabetes, multiple sclerosis, osteoporosis, fertility, asthma etc.[2,3] Thus, vitamin D_3 has brought an incredible amount of attention towards health care professionals. Since inflammation is a key component in the pathophysiology of asthma, anti-inflammatory drugs especially corticosteroids are typically prescribed. Vitamin D was also found to be anti-inflammatory in many tissues and lung tissue also one among. Vitamin D significantly decreases regulated on activation, normal T cells expressed and secreted

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(a proinflammatory molecule that attracts monocytes, T cells and eosinophils) and IP-10 (a proinflammatory mediator that recruits activated T cells, mast cells and natural killer cells).[4]

Despite a day-to-day foods are fortified with vitamin D, many studies have shown an absolute deficiency of vitamin D in many people. Vitamin D deficiency leads to increased bronchial hyper responsiveness and reduced pulmonary function.[5] Nearly, 5-15% of patients with asthma symptoms and exacerbation are uncontrolled despite of routine controller medications including corticosteroids. Therefore, they are more prone to have irreversible obstruction of airflow and also associated with airway remodeling.[6,7] If vitamin D plays either preventive or protective role against the development of asthma, then it could be the most effective therapy.

Very few studies[8,9] have considered this point and evaluated the relationship between vitamin D_3 and pulmonary function and there is no clinical study report from Indian adult population to explore the role of vitamin D_3 in asthma. Thus, the present study was undertaken to study whether or not vitamin D_3 can improve pulmonary function in mild to moderate persistent asthma patients.

MATERIALS AND METHODS

Study protocol and recruitment

The study was approved by the Institutional Ethical Committee (330/IEC/2012) and it was undertaken in Pulmonary Medicine department in SRM Medical College hospital and research center, Kattankulathur, Tamil Nadu, India. The study was conducted according to the International Conference for Harmonization good clinical practice guidelines, 2008 amendment. This is a randomized, open-labeled, pilot study. A total of 63 patients completed the study. Patients were aged between 35 and 65 years, either sex, without co-morbidities and mild to moderate persistent condition were included in the study. Patient with a history of cardiac disorders, chronic obstructive pulmonary disease, pregnant women and lactating mothers, significant hepatic and renal dysfunction, intolerance to vitamin D supplementation and voluntary withdrawal were excluded from the study. Written consent was obtained from all the patients.

Study design

Patients satisfying above study criteria were enrolled in the study. Enrolled patients were randomized by randomization chart generated by computer assisted random allocation procedure. Patients were divided into two groups namely usual care (n = 31) and intervention care (n = 32) groups. Clinical information relevant for the study was collected from the patients, health-care professionals, necessary records and as well as from patient's bystanders in few cases. Anti-asthmatic drugs prescribed until date were stopped and the patients were asked to take salbutamol inhaler (i.e., rescue medication) whenever necessary for a 7-day (run-in period) prior to the study. Patients were educated and counseled about the proper usage of inhalers. Usual care group patients received budesonide 400 μg with formoterol 24 μg daily. This is the fixed dose combination (FDC). One puff contained 200 μg budesonide and 6 μg formoterol. Patients had taken two puffs morning and two puffs night. Intervention care group patients received the same FDC plus vitamin D_3 tablet (1000 IU). All patients could take short acting β-agonist in case of an asthmatic crisis. All the patient's clinical symptoms and pulmonary function (forced expiratory volume in 1 s [FEV_1] by spirometry) were measured at baseline and every follow-up days, i.e., day 30, 60 and 90. Each and every follow-up, patient medication adherence and their inhaler usage technique were monitored.

Statistical analysis

A sample size of not less than 30 was considered for this pilot study. Data are expressed as mean ± standard deviation The $P < 0.05$ was considered for statistical significance. Demographic characteristics such as age and gender, baseline and final visit data were used to assess response rates by comparing usual care and intervention group. Student's t test was used for the comparisons within the groups. One-way analysis of variance Bonferroni multiple comparison test was used for comparisons between groups using Graph Pad Software, Inc., (USA). Per protocol analysis has performed.

RESULTS

A total of 90 patients attended the screening phase for mild to moderate asthma condition, out of which 68 patients met the study criteria. Patients who got enrolled after giving informed consent were randomized into two groups. In the usual care group, out of 33 patients, 31 patients completed the study and in the intervention care group, out of 35 patients, 32 patients completed the study. Reasons for drop out in both groups were mentioned in Figure 1.

In the usual care group, out of 31 patients, 15 patients were male and 16 patients were female and their mean age was 56.23 ± 8.1 years, mean body mass index (BMI) was 21.6 ± 2.8. Out of 32 patients in intervention care group, 14 patients were male and 18 were female and their mean age was 57.26 ± 8.0 years, mean BMI was 20.4 ± 3.3. No significant difference was observed in age, BMI and gender distribution between the study groups [Table 1].

In the usual care group, 22.6% ($n = 7$) and in the intervention group, 25% ($n = 8$) patients were found as coolies. In both groups, 16.1% and 12.5% patients were employed and 16.1% and 15.6% were self-employed respectively. There was no patient in both groups were professional workers. Patients in others category included housewives in both groups. The educational status of the patients was also shown in Table 1. 16.1% ($n = 5$) patient with usual care and 21.9% ($n = 7$) patients in intervention care group were illiterate. 13 and 14 patients (41.9% and 43.8%) in usual and intervention care group studied between 1st and 10th standard. 38.7% ($n = 12$) and 34.4% ($n = 11$) in usual and intervention care group patients had an 11th standard to a degree education. No patient in intervention care and 3.2% ($n = 1$) in the usual care group had post-graduation qualification.

The changes in the percentage FEV_1 values from baseline (day 0) to end of the study (day 90) in both groups are shown in Table 2. It is evident from the table that FEV_1 values are improved at every follow-up in both groups. The percentage improvement in FEV_1 from baseline to end visit between the groups were shown in Table 3. For the usual care group patients, the mean difference was 4.95 with the confidence interval (CI) of 0.2755-9.624. There was significant ($P < 0.05$) improvement in percentage predicted FEV_1. Intervention group patients, the mean difference were 7.07 with the CI of 2.469-11.67. Significant ($P < 0.001$) improvement in percentage predicted FEV_1 after 90 days treatment was observed in the intervention groups. There is no statistically significance were observed between the groups.

Physical examination including oropharyngeal inspection, heart rate and blood pressure were monitored for study patients. There were no significant changes in such

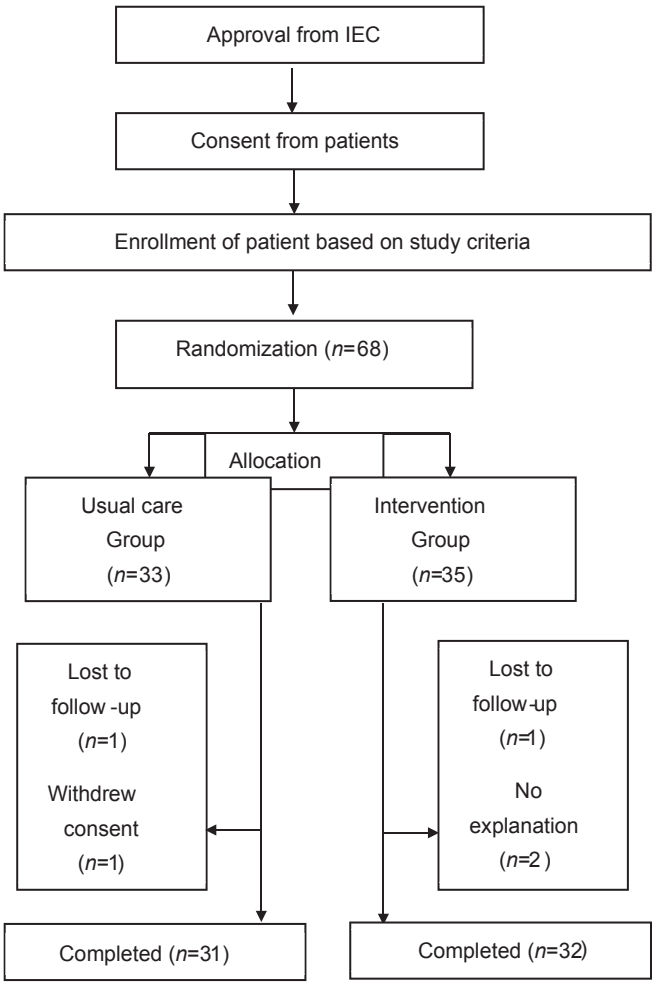

Figure 1: Flow of patients and CONSORT Diagram

Table 1: Demographic data of the patients

Demographic variables	Usual care (*n*=31)	Intervention care (*n*=32)
Age (in years) (mean±SD)	56.23±8.1	57.26±8.0
BMI (mean±SD)	21.6±2.8	20.4±3.3
Gender % (*n*)		
Male	48.4 (15)	43.8 (14)
Female	51.6 (16)	56.3 (18)
Treatment		
Medications	Budesonide 400 µg+formoterol 24 µg	Budesonide 400 µg+formoterol 24 µg+vitamin D3 1000 IU
Pulmonary function		
FEV_1	69.90±8.56	68.71±7.56

SD=Standard deviation, FEV_1=Forced expiratory volume in 1 s, BMI=Body mass index

Table 2: Visit wise changes in % predicted FEV_1 between the groups

Group	% predicted FEV_1			
	Day 0 (baseline)	Day 30 (FU1)	Day 60 (FU2)	Day 90 (FU3)
Usual care	69.90±8.56	71.23±7.96^{ns}	72.45±5.48^{ns}	74.85±6.75*
Intervention care	68.71±7.56	72.32±6.42^{ns}	74.48±5.64**	75.78±6.42***

Data expressed as mean±SD, Paired *t*-test, GraphPad Prism, version 6.0, day 0, USA. versus day 30, 60 and 90 in each group, ns=Not significant, *P<0.05, **P<0.01, ***P<0.001, SD=Standard deviation, FEV_1=Forced expiratory volume in 1 s

Table 3: Comparison of % FEV_1 between day 0 and 90 among the study groups

Group	% predicted FEV_1		Mean difference	*P* value	95% CI
	Day 0	Day 90			
Usual care	69.90±8.56	74.85±6.75	4.950	<0.05	0.2755-9.624
Intervention care	68.71±7.56	75.78±6.42	7.070	<0.001	2.469-11.67

FEV_1=Forced expiratory volume in 1 s, CI= Confidence interval

assessments recorded in all the clinical visits compared with baseline values (data are not shown). Asthma exacerbations, which required hospitalization, were considered as serious adverse events. There was no such critical situation faced by study patients of both groups.

DISCUSSION

Pharmacotherapy is essential for asthma management and is based on stepwise treatment for different levels of asthma severity: Intermittent, mild persistent, moderate persistent and severe persistent. Antiasthma drugs are classified into the controller and preventive medications. Among the controller medications, an inhaled corticosteroid (ICS) is the mainstay and the use of ICS is considered as one of the best treatment options for patients with mild to moderate asthma condition.[10] However, not all the patients achieve the asthma treatment goal with corticosteroid, because, asthma is a multi-factorial disease where inflammation alone is not playing the role. The pathophysiology of asthma is complicated. Recent data indicate that current pharmacotherapy for asthma is inadequate to control asthma.[11] Therefore, there is a need to identify the cause of asthma and treatment should be aimed at the identified risk.

Studies carried out in an animal model reported that vitamin D_3 pre-treated groups enhanced the efficacy of allergen immunotherapy in a mouse allergic asthma model.[12] Bergman *et al.*,[13] 2012 studied the effect of vitamin D_3 supplementation to reduce the disease burden in patients with frequent respiratory tract infection. They evidenced their report from both per protocol analysis and intention-to-treat models.

Gergen *et al.*, 2013[9] examined the relationship between serum vitamin D_3 levels and allergic diseases. They found that higher the serum vitamin D_3 concentration, lower in total IgE levels and peripheral eosinophil counts. Black and Scragg[14] also revealed a strong relationship between serum concentration of vitamin D_3 and pulmonary function parameters like FEV_1 and forced vital capacity.

Iqbal and Freishtat 2011[15] analyzed the various factors and the role of vitamin D_3 in asthma. They concluded that vitamin D_3 acts on lung tissue and to improve immune function and reduce inflammation. However, they did not give any ample evidence that vitamin D_3 has the potential to improve pulmonary function. Studies carried out in pediatric population[16] also not reported any definitive proof of improved clinical symptoms of asthma with the adjunctive therapy of vitamin D_3. Recently Gergen *et al.*, 2013[9] studied the relationship between serum vitamin D_3 concentration and prevalence of asthma with severity and response of asthma treatment. The study concluded that overall vitamin D_3 concentrations were low in two samples of adolescents and they were not reliably linked with the presence of asthma or asthma morbidity.

From the above contradictory statement, we could not come to a conclusion whether vitamin D_3 has a role on asthma condition or not. Thus, the present study was undertaken and the study was designed as open-labeled, randomized trial.

Dupont *et al.* 2005[17] observed an improvement in pulmonary function and asthma symptoms with add-on leukotriene receptor antagonist therapy, for a period of 2 months in an open- labeled study with insufficiently controlled asthma patients with ICS and long-acting β_2 agonists as FDC. Shah *et al.*, 2006; Korn *et al.*, 2009; Keith *et al.*, 2009[18-20] studied the effectiveness of controller medications as add on therapy to ICS, in improving lung functions and asthma symptoms. All these studies were carried out for a period of 8 weeks. With this background, a period of 90 days study duration in the present study was relatively considered to be sufficient to identify the effectiveness of study medications along with vitamin D_3 supplementation. However, this may be the limitation of this study, since the present study could not measure the asthma exacerbations in the long-term control. The study is designed as an open-label study. This may be another weakness of the study, but in routine clinical practice, blinding of the drug is not appropriate and the data obtained are suitable to real life setting.

The present study did not measure the level of vitamin D_3 in the blood. This is the major limitation of the study. Future studies can be directed towards this direction. Nevertheless, our study has some special features. For instance, we gave 1000 IU vitamin D_3 as a daily dose. Other studies used lower doses of vitamin D_3[21-24] and importantly, there are no clinical data on mild to moderate persistent asthma patients especially from the south Indian population. Thus, supplementation of vitamin D_3 in asthma is an innovative tactic in improving pulmonary function.

The finding of this suggests that the addition of vitamin D_3 to the regular treatment regimen improves pulmonary function. In recent days, an important talk and task among the researchers is to find the exact mechanism through which vitamin D_3 exerts its pharmacological action on bronchial airways. However it is very complicated to retort the above. Vitamin D_3 acts on numerous ways to control asthma[25-28] and the important ways are: It inhibits bronchial smooth muscle cell proliferation and remodeling and thereby, inhibits the synthesis and release of cytokines. Vitamin D_3 acts on mast cells and inhibits the differentiation and maturation of mast cells and down-regulate the expression of CD4+ and CD8+ cells

to allergic airways. Vitamin D_3 enhances interleukin-10 and transforming growth factor-β synthesis by acting on dentric and regulatory cells respectively.

In the present randomized, open-labeled study there is an evidence for improvement in pulmonary function clinically as well as statistically on supplementation of vitamin D_3. If the dietary intake of vitamin D fails to meet the recommended daily allowance, health-care professionals may encourage the asthma people to increase their intake of vitamin D, preferably through the consumption of healthy food sources rich in vitamin D or otherwise through the use of appropriate vitamin supplements. However, considering an open-label design, future studies may be directed toward longer duration followed by serum estimation of serum 25-hydroxy vitamin D to substantiate the current findings.

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