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Does Dose Reduction of an Inhaled Corticosteroid with the Addition of Leukotriene Antagonist is Clinical Significance in Asthma Patients? A Randomized Clinical Trial

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Abstract: Asthma is an inflammatory disease characterized by recurrent episodes of breathlessness and wheezing. Though inhaled corticosteroids (ICS) play a vital role in the treatment of asthma, it has commendable side effects. Reduction of ICS dose with any other drug combination may therefore be of clinical significance. A total of 108 patients with mild to moderate asthma were enrolled in this randomized controlled study from respiratory medicine department of a tertiary care hospital. Patients were randomized into two groups viz., usual care (n=54) and intervention group (n=54). Usual care group patients received Budesonide. Patients in the intervention group received Montelukast with half of the dose of Budesonide. Pulmonary function test was assessed at the baseline and on follow up days. No significant difference was observed with respect to socioeconomic and educational status of patients between usual care and intervention group. Significant ($P<0.01$) improvement in FEV_1 after 150 days treatment with Montelukast and half dose of steroid was observed. There is no serious adverse drug reaction among the tested groups. The study concluded that dose reduction of an inhaled corticosteroid with the addition of leukotriene antagonist is clinically significant in asthma patients. The future studies may be directed towards extended duration of action.

Key words: Montelukast · Asthma · Budesonide · Spirometer

INTRODUCTION

Asthma is an inflammatory disease characterized by recurrent episodes of breathlessness and wheezing, which vary in severity and frequency from person to person. It is due to inflammation of the bronchial airway in the lungs which affects the sensitivity of the nerve endings in the airways so they become easily irritated. This inflammation also leads to narrowing of airways and thereby reducing the air flow in and out of the lungs [1]. According to world health organization (WHO) statistics, asthma affects 300 million people and its prevalence increases globally by 50% every decade [2].

The goals of asthma therapy are to achieve asthma control (i.e.) near normal lung function, absence of asthma symptoms, no activity limitations and no episodes of worsening asthma [3]. Twice daily doses of an inhaled corticosteroid (ICS) are main choice for nearly all types of asthma patients. Starting with an intermediate dose and then to diminish the dose (Step down therapy) when symptoms are controlled after 3 months is in general practice [4]. If symptoms are not controlled, a Long acting beta agonist (LABA) is added (Step up therapy), most suitably by switching to a combination inhaler [5]. The dose of controller medications should be accustomed accordingly, as judged by the need for a rescue inhaler. ICS plus LABA combination become a gold standard combination for asthma patients and it is recommended by the Global Initiative for Asthma (GINA) guideline as a first line treatment regimen [6,7].

However many patients with persistent asthma cannot attain all the above treatment goals with this gold standard combination. Therefore, finding a new treatment regimen is always a welcome sign. The present study is

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aimed to compare the effect of higher dose of ICS, low dose ICS plus leukotriene antagonist in mild to moderate persistent asthmatic patients. This kind of study in Indian population would benefit the health care providers in choosing the appropriate medication to treat asthma.

MATERIALS AND METHODS

Study Protocol and Recruitment: The study was approved by the Institutional Ethical Committee (190/IEC/2011) and it was undertaken at Pulmonary Medicine department in SRM Medical College hospital and research center, Kattankulathur, Tamil Nadu, India. This is a randomized open label study. A total of 108 patients completed the study. Patients were aged between 18 to 65 years, either sex, without co-morbidities and mild to moderate persistent condition were included in the study. Patient with history of cardiac disorders, COPD, pregnant women and lactating mothers, significant hepatic and renal dysfunction and voluntary withdrawal were excluded from the study. Written consent was obtained from all participants.

Sample Size Calculation: Considering α error at 0.05 and 80% power ($1-\beta = 0.8$) of study with an approximate 7.6% difference between two groups for a significant increase in pulmonary function with the standard deviation of 0.05 using 1:1 ratio of independent sample t-test, 54 patients must complete the study in each group. Considering 20% dropout, 64 patients should be included in each group.

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 group (n=54) and intervention group (n=54). Clinical information relevant for the study was collected from the patients, healthcare professionals, necessary records and as well as from patient's bystanders in few cases. Antiasthmatic drugs prescribed till 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.

Patients who were in the usual care group, received Budesonide 400µg twice a day (bid) and intervention group patients received Budesonide 200µg twice a day (bid) plus tablet Montelukast 10mg for a period of six months. All patients could take short acting β-agonist in case of an asthmatic crisis. Patient's pulmonary function test (FEV_1 by spirometry) and clinical symptoms were measured at the baseline and every follow up days i.e. day 30, 60, 90, 120 and 150. Each and every follow up, patient medication adherence and their inhaler usage technique were monitored.

Pulmonary Function Test: Pulmonary function test (PFT) was performed with spirometry. Spirometry is the measurement of flow of air into and out of the lungs. The patient's age, gender, race, height and weight were measured before the procedure begins. The patients were instructed not to eatheavily within three hours of the test and to wear loose-fitting clothing over the chest and abdominal area while coming for test. The respiratory therapist or other testing personnel explained and demonstrated the breathing maneuvers to the patient. Spirometry test was performed with a spirometer, which consists of a mouthpiece and disposable tubing connected to a machine that records the results and displays them on a graph. Patients inhaled deeply and closed the mouth tightly around the tube and then exhales through the tubing while measurements were taken. The volume of air inhaled or exhaled and the length of time each breath takes were recorded and analyzed. Nose clips were usually used to make sure air is only coming out of the mouth. Sometimes a test was repeated to get the best and maximum effort.

Statistical Analysis: Data are expressed as mean ± SD. The probability value less than 0.05 was considered for statistical significance. Demographic characteristics like 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 ANOVA Bonferroni multiple comparison test was used for the comparisons between groups using GraphPad Software, Inc. (USA)

RESULTS

A total of 141 patients attended the screening phase for mild to moderate asthma condition, out of which 128 patients met the study criteria. The patients who got enrolled after giving informed consent was randomized into 2 groups to receive usual care and intervention care treatment. Flow chart representing patient distribution is illustrated in Fig.1.

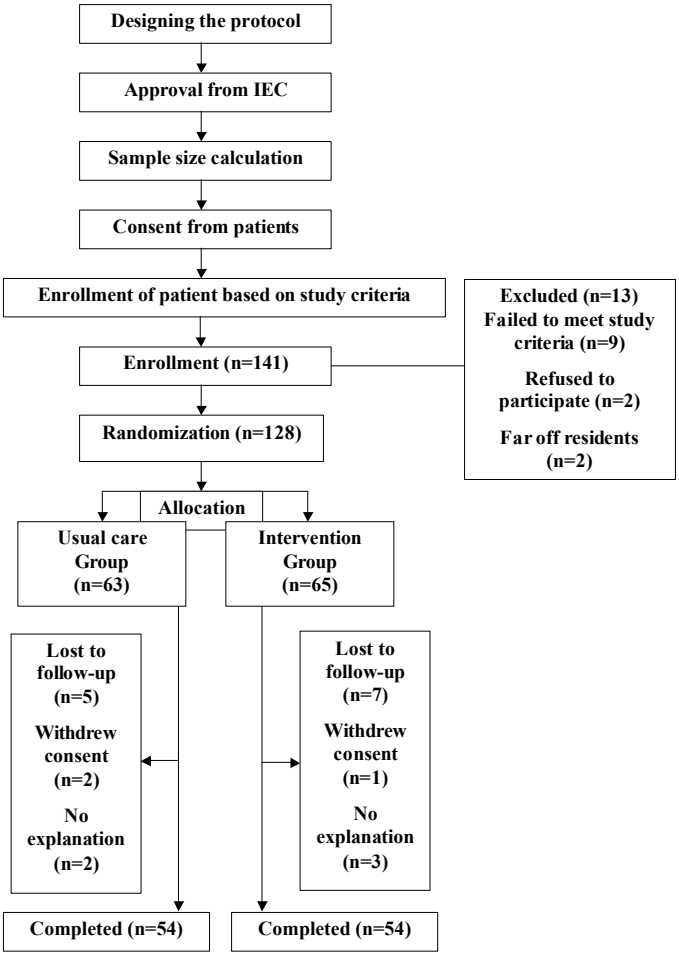

Fig. 1:

In the usual care group out of 54 patients, 37 patients were male and 17 patients were female and their mean age was 55 ± 8.1 years, mean BMI was 25.3 ± 3.4. Out of 54 patients in intervention group 39 patients were male and 15 were female and their mean age was 54 ± 8.0 years, mean BMI was 24.9 ± 2.5. No significant difference was observed in age and BMI between the study groups (Table 1).

No patient was found less than one year of disease duration history. About 68.5% (n=37) and 62.9% (n=34) had a disease history of one to five years in usual and intervention care groups respectively. Another 20.3% (n=11) and 11.1% (n=6) had 5-10 years and more than 10 years of disease duration in the usual care group. Whereas 24.0% (n=13) and 12.9% (n=7) patients in intervention care group had the disease history of five to ten years and more than ten years respectively.

24.0% (n=13) and 29.6% (n=16) patients from usual care and intervention care group were found as coolies respectively. 22.2% (n=12) in the usual care group and 20.3% (n=11) in intervention care group were employed. 27.7% (n=15) and 22.2% (n=12) were self-employed in usual care and intervention care group respectively. 7.4% (n=4) in group 2 and no patient in group 1 was professional. 24.0 % (n=13) and 20.3% (n=11) patients were in others category that include housewives in both groups respectively.

The educational status of the patients was also shown in Table 1. No patient with usual care and 16.6% (n=9) patients in intervention care group were illiterate. Twenty four and twenty two patients (44.4% and 22.0%) in usual and intervention care group finished first standard to tenth standard. 55.5% (n=30) and 38.8% (n=21) in usual and intervention care group patients had an eleventh standard to a degree education. No patient with usual care and 3.7% (n=2) in the intervention group had post-graduation qualification.

Table 1: Demographic data of the patients

Demographic Variables	Usual care (n=54)	Intervention care (n=54)
Age (in years)		
(Mean ± SD)	55.17 ± 8.1	54.35 ± 8.0
BMI (Mean ± SD)	25.3 ± 3.4	24.9 ± 2.5
Gender % (n)		
Male	68.5% (37)	72.2% (39)
Female	31.4 % (17)	27.7% (15)
Duration of disease % (n)		
<1 year	0% (0)	0% (0)
1-5 years	68.5% (37)	62.9% (34)
5-10 years	20.3% (11)	24.0% (13)
>10 years	11.1 % (6)	12.9% (7)
Socioeconomic Status % (n)		
Coolie	24.0% (13)	29.6% (16)
Employed	22.2% (12)	20.3% (11)
Self Employed	27.7% (15)	22.2% (12)
Business	1.8% (1)	0% (0)
Professional	0% (0)	7.4% (4)
Others	24.0% (13)	20.3% (11)
Educational Status % (n)		
Illiterate	0% (0)	16.6% (9)
1 to 10	44.4% (24)	40.7% (22)
11 to degree	55.5% (30)	38.8% (21)
>degree	1.8% (1)	3.7% (2)

The changes in the mean FEV_1 values in the usual care and the intervention group from the baseline to the end of the study are shown in Table 2. It is evident from the results that FEV_1 values are improved at every follow up. In the intervention group, there is a significant ($P<0.01$) improvements in FEV_1 % predicted value when compared the baseline and final visit value. No statistical significant difference was observed in the usual care group. (Table 3).

Physical examination including oropharyngeal inspection, heart rate and blood pressure were monitored for study patients. There were no significant changes in such assessments recorded in all the clinical visits compared to baseline values.

Asthma exacerbations which required hospitalization were considered as serious adverse events. There was no such critical situation faced by study patients of both groups. It portrayed that both group patients were well controlled by their treatment regimens. There were no significant differences in the number of adverse drug reactions between the treatment groups. A total of 14 adverse drug reactions were reported in the usual care group and 9 were in the intervention group.

Table 2: % FEV_1 values for usual care and intervention group patients

Groups	Baseline Value (Day 0)	First follow up (Day 30)	Second follow up (Day 60)	Third follow up (Day 90)	Fourth follow up(Day 120)	Fifth follow up (Day 150)
Usual care Group	63.00±9.14	65.15±8.32	67.76±8.96	69.15±8.32	73.76±8.96	75.03±8.55
Intervention Group	63.24±4.05	68.44±6.52	72.21±7.06	76.44±6.52	78.21±7.06	80.03±8.74

Table 3: Comparison of % FEV_1between Day 0 and 150 among the study groups

	% Predicted FEV_1				
Groups	Day 0	Day 150	Mean difference	P Value	95% CI
Usual care group	63.00±9.14	75.03±8.55	-0.240	P>0.05	3.626 to -4.106
Intervention group	63.24±4.05	80.03±8.74	5.000	P<0.01	1.134 to 8.866

Data expressed as mean ± SD

Paired t-test

GraphPad Prism.

Table 4: Adverse drug reactions in study groups

S. No.	ADRs	Usual care group	Intervention group
1	Asthma Exacerbation	0	0
2	Tremor	6(11.11)	5(9.09)
3	Dizziness	2(3.7)	0
4	Cough	1(1.85)	2(3.63)
5	Palpitation	1(1.85)	0
6	Nausea / Vomiting	0	1(1.81)
7	Dyspepsia	1(1.85)	1(1.81)
8	Oral candidiasis	1(1.85)	0
9	Insomnia	1(1.85)	0
10	Bronchospasm	1(1.85)	0

When the adverse drug reactions were documented and analyzed it was found that tremor was the most common adverse effects observed in both the groups. Other minor effects reported were cough, dizziness, palpitation, nausea/vomiting, dyspepsia, oral candidiasis, insomnia and bronchospasm. According to Naranjo's scale, it was confirmed by a panel of judges that most of the adverse drug reactions were possibly related to the study medications. Various adverse reactions reported by patients in all the study arms were noted and are shown in Table 4.

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 [8]. Common antiasthma medications include corticosteroids (inhalation and oral), long acting-beta2 agonists (LABA), Cromolyn sodium or Nedocromil sodium, Methylxanthines and Leukotriene modifiers (LT-M) [9, 10].

The use of ICS is considered as one of the best treatment options for patients with mild to moderate asthma condition [11]. Anti-inflammatory action of ICS in the lungs is well established and ICS has proven its efficacy in improving pulmonary function and reducing exacerbations of asthma [12]. However, increasing the dose of inhaled corticosteroid may produce number of potential side effects [13]. Moreover, higher dose of inhaled corticosteroid may not necessarily result in adequate control of asthma symptoms for all patients [14] because corticosteroids do not utterly inhibit either synthesis or release of cysteinylleukotrienes in the lungs.

The cysteinylleukotrienes especially LTC_4, LTD_4 and LTE_4 induce many pathological changes in lungs including airflow obstruction, mucus secretion and inflammatory cell infiltration. Thus, anti-leukotriene agents have beneficial action. International guidelines suggest that the inhaled corticosteroid dose should be reduced whenever possible [15]. The addition of a second agent with sufficient asthma controlling power may therefore be useful. The finding of this study suggests that the addition of Montelukast to the inhaled corticosteroid promotes a comparable asthma control to doubling the dose of Inhaled corticosteroid with enhanced onset of action and lesser potential adverse effects [16, 17].

A previous report indicated that compliance with inhaled medications was inferior to that with oral medication [18, 19]; multiple daily administration of any therapy also contributes to poor compliance [20]. An oral therapy administered once daily could potentially provide the clinical efficacy requested in common clinical practice. The study data demonstrated that Montelukast provided an important effect on bronchial responsiveness in patients with mild-moderate persistent asthma. Montelukast may offer clinical benefits due to a better compliance and the advantage of reducing the dose of ICS while maintaining symptom control thus minimizing possible ICS adverse effects. Corticosteroids are not capable of completely blocking the pro-inflammatory effects of cysteinyl leukotriene. In addition it has been demonstrated that the pharmacological mechanism of action of Montelukast is different from and complementary to that of ICS.

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