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Research Article

A prospective, open labeled, comparative study to assess the efficacy of montelukast as add on to β_2-agonist and inhaled corticosteroid in patients of moderate persistent asthma

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ABSTRACT

Background: Steroid, bronchodilator and the leukotriene receptor antagonist montelukast have demonstrated efficacy in children with mild persistent asthma, but comparative long-term studies in adult patient with moderate persistent asthma is needed. A randomized and prospective study was undertaken to find out the efficacy of montelukast as add on to β_2-agonist and inhaled corticosteroids in patients of moderate persistent asthma.
Methods: This was a continuous, longitudinal, prospective study carried out at a tertiary care teaching hospital. Newly diagnosed patients of moderate persistent asthma attending the chest out patient department (OPD) were enrolled. Group I was treated with salbutamol 200 mcg rotacap SOS and formoterol 6 mcg + budesonide 400 mcg rotacap BD. In addition to these medicines group II also received montelukast 10 mg OD. The patients were followed up every two months. Clinical examination and pulmonary function tests (PFT) were carried out at baseline and during each visit. Unpaired 't' test was used for statistical analysis.
Results: Comparison of clinical symptoms revealed a better improvement in group II as compare to group I [cough - 83% vs. 33%; breathlessness - 75% vs. 33%; and wheezing - 83% vs. 78%] at the end of one year. A significantly better ($p < 0.05$) improvement in forced expiratory volume (FEV_1) was also observed in group II.
Conclusions: Treatment with montelukast leads to better improvement in clinical symptoms and PFT in the patients of moderate persistent asthma.

Keywords: Moderate persistent asthma, Salbutamol, Montelukast, Pulmonary function test (PFT)

INTRODUCTION

In India, the prevalence of asthma had been about 2 to 3%. However, the incidence is rising that appears to be associated with increased urbanization and air pollution A study conducted in Lakeside Medical Centre and Hospital on 20,000 children under the age of 18 years from 1979, 1984, 1989, 1994 and 1999 in the city of Bangalore showed a prevalence of 9%, 10.5%, 18.5%, 24.5% and 29.5% respectively.[1] The persistent asthma also showed an increase from 20% to 27.5% and persistent severe asthma 4% to 6.5% between 1994 to 1999.[1]

It has been well known that bronchial asthma is chronic inflammatory airway disease, characterised by complex interaction of airway hyperresponsiveness, bronchoconstriction and respiratory symptoms. According to American college of allergy, asthma and immunology (ACAAI), bronchial asthma is classified into mild, moderate and severe category. The classification is based on the frequency, severity of clinical symptoms and impairment in pulmonary function tests especially forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF).[2]

The goal of asthma therapy is to achieve clinical control and near normal lung functions. Traditionally, symptomatic control of bronchoconstriction has been achieved by the use of bronchodilators. The growing evidence of bronchial asthma being an inflammatory condition has resulted a paradigm shift in asthma medications to the use of anti-inflammatory agents like

glucocorticoids. Research into asthma pathophysiology has specified the role of leukotrienes as one of the proinflammatory agents in bronchial asthma. The cysteinyl leukotrienes LTC4, LTD4, and LTE4 induce many of the pathophysiological changes in the lungs of asthma patients including airflow obstruction, mucus hypersecretion, inflammatory cell infiltration and act as chemo attractants for eosinophils in the airway. Thus leukotriene receptor antagonists like montelukast reduce airway inflammation and ameliorate asthma symptoms.

Conventionally, the drug treatment of bronchial asthma has been categorized as short term "relievers" and long term "controllers". Short-acting β_2-agonist (SABA), such as salbutamol with maximal bronchodilatation by 30 minutes and persists for 3-4 hours, is used for short term symptomatic relief. Long-acting β_2-agonists (LABA) like salmeterol and formoterol achieve long duration of action (12 hours) and improve asthma control. Inhaled glucocorticoids, such as beclomethasone dipropionate, budesonide, and fluticasone propionate, are used to control inflammatory pathology in persistent asthma. Several clinical trials have been conducted to investigate the effect of inhaled corticosteroids (ICS) in combination with LABA therapy.[3] These studies have reported that inhaled corticosteroids and long acting β_2 adrenergic receptor agonist improve lung function and decreased dependence on short-acting β_2 adrenergic receptor agonist therapy. In addition, the combination therapy also allowed asthma to be controlled at lower doses of corticosteroids. This observation has led to the widespread use of fixed dose combination inhalers that contain a corticosteroid and LABA, which have proved to be highly effective in the control of asthma. Asthmatic patients maintained on inhaled glucocorticoids show improvement in symptoms and lowered requirements for "rescue" with β_2 adrenergic agonists. Few clinical trials have also demonstrated additive effect of leukotriene antagonists thereby improving asthma control and lung functions.[4] Several studies have recommended the use of montelukast in pediatric patients as monotherapy for mild persistent asthma or as add on therapy to ICS for moderate to severe persistent asthma.[5] However, there is little published information comparing LABA or SABA with or without leukotriene antagonist montelukast on clinical symptoms and pulmonary function tests especially in adult Indian patients. Thus we conducted a study to find out the efficacy of montelukast as add on to β_2-agonist and inhaled corticosteroid in patients of moderate persistent asthma.

Civil Hospital, Ahmedabad is a tertiary care, multispecialty, teaching hospital with 2000 beds, a daily patient turnover of approximately 2000 outdoor patients and an outpatient turnover of 7.5 lakhs annually. The hospital caters to patients from the states of Gujarat, parts of Rajasthan and Maharashtra. Department of Tuberculosis and Chest Disease form a significant proportion in providing the medical services and undertaking research activities. The department has also collaboration with central Government institutions like Indian Council of Medical Research (ICMR) and National Institute of Occupational Health (NIOH) in this regard.

METHODS

A continuous, longitudinal, prospective, observational, single centre study was carried out in outpatients of bronchial asthma attending Tuberculosis (TB) and Chest Disease Department, Civil Hospital, Ahmedabad. Prior permission to conduct the study was obtained from Institutional Ethics Committee, the Medical Superintendent and Head of TB and Chest Disease Department. Informed consent was obtained from all patients enrolled in the study. The investigator visited the outpatient department (OPD) daily from 9:00 am to 12:00 noon and enrolled all newly diagnosed patients of bronchial asthma based on inclusion and exclusion criteria as follows:

Inclusion criteria:

- As per Global Initiative for Bronchial Asthma (GINA) guidelines[6], newly diagnosed patients of moderate persistent asthma attending OPD of Tuberculosis & Chest Disease at Civil Hospital, Ahmedabad.
- All patients in the age of 12 to 50 years, of either gender.
- Patient willing to participate and give informed consent.

Exclusion criteria:

- Patients of mild asthma, severe asthma and status asthmaticus.
- Patients having concomitant medical disorders like cardiac disease, hypertension, etc.
- Patients not willing to participate or refuse to give consent.

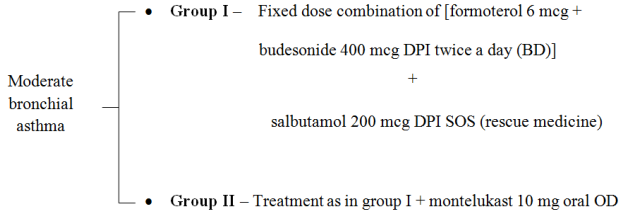

Figure 1: Drug treatment in Group I and II.

The patients were examined and diagnosed as moderate asthma by the physician as per clinical presentation and pulmonary function tests.[6] Patients having clinical

symptoms daily and forced expiratory volume in 1 second more than 60% but less than 80 % predicted were categorized as moderate asthma. The patients of moderate asthma were categorized into group I and II according to their drug treatment as shown in figure 1.

The study was conducted over a period of 24 months from October 2009 to September 2011. At the first visit, after detailed history a baseline clinical symptomatology and pulmonary function tests were done. Subsequent follow up visits after 8 weeks, patients were assessed for clinical symptoms and pulmonary function tests were repeated. The pulmonary function tests were performed by MIR's Spirometer (MIR spirolab, Italy) where flow measurements were done by bi-directional digital terbium followed by computerized analysis. All patients were followed up every two months for subsequent six visits. A case record form (CRF) was designed and pretested in ten patients and modified suitably. The case records were reviewed and the relevant information was written in a pretested CRF. Additional information was obtained from the patients and relatives.

Following details were recorded in CRF:

- General information including name, age, gender, weight, height, address, monthly income, occupation, accompanying person and transportation cost.
- Chief complaints like cough, wheezing and breathlessness.
- Personal history such as smoking, sleep disturbance, no. of attacks per month, no. of nocturnal awakening per month, frequency of inhaled short acting β_2- agonist per month and concomitant medical diseases.
- Past history of allergic diseases, tuberculosis, etc.
- Family history of bronchial asthma or allergic disease.
- Clinical examination like temperature, pulse rate, blood pressure, respiratory rate, cyanosis and pallor.
- Systemic examination.
- Laboratory investigations including haematological test, biochemical test and radiological test.
- Pulmonary function tests (PFTs) such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), forced expiratory flow 25-75% (FEV_{25-75}), forced expiratory volume 1% (FEV_1%).
- Drug treatment - details of all drugs including brand name, generic name, dose, route, frequency of administration and cost per therapy.

Study end points:

- Clinical improvement in symptoms of bronchial asthma.

- Improvement in pulmonary function tests.

Unpaired 't' test was used for statistical analysis.

RESULTS

Baseline

The patients were allotted to two groups on the basis of drug treatment. Data show that out of 45 patients with moderate bronchial asthma, there were 30 men and 15 were women. The mean age of patients in group I and II was 27.2 ± 5.9 and 24.7 ± 6.1 years respectively. The age of patients in both groups was comparable. Mean weight of patients in group I and II was 58.0 ± 6.2 and 57.1 ± 4.9 kg respectively. Mean height of patients in group I and II was 158.3 ± 6.4 cm and 158.7 ± 7.7 cms respectively. The weight and height of patients in all groups were comparable. Details of general characteristics of patients are shown in table 1.

The most frequent presenting complaints of patients were breathlessness followed by cough and wheezing. The detail of clinical symptoms of both groups is shown in table 2 & 3. The baseline values of pulmonary function tests including mean forced expiratory volume in 1 second (FEV_1), forced expiratory flow 25-75% ($FEV_{25-75\%}$), peak expiratory flow rate (PEF) and forced expiratory volume in 1% ($FEV_{1\%}$) of group I and II was shown in table 4.

Follow-up

Clinical symptoms:
The patients were followed up every two months for clinical symptoms and PFTs. There was significant improvement (p<0.05) in breathlessness and cough in both groups at first follow up. However, wheezing improved in group I at second follow up. The details of clinical symptoms of each group at each follow up are shown in table 5 and figure 2.

Moreover, there was significant reduction (p<0.05) in frequency of nocturnal awakening and inhaled short acting β_2-agonist per month at 1st follow up as compared to baseline in group II only. The number of nocturnal awakening significantly reduced (p<0.05) at second follow up in group I. The details are shown in table 6 and figure 3, 4. Further, the symptoms in patients of group I

and II continued to improve significantly (p<0.05) till the end of study.

Table 1: General characteristics of the patients with moderate asthma in the study.

Parameter	Moderate bronchial asthma	
	Group I	Group II
Number of patients	26	19
Mean age (Years)	27.2 ± 5.9	24.7 ± 6.1
Gender Men Women	 17 9	 13 6
Mean weight (kg.)	58.0 ± 6.2	57.1 ± 4.9
Mean height (cms.)	158.3 ± 6.4	158.7 ± 7.7
Treatment	FDC of [Formoterol 6 mcg + Budesonide 400 mcg DPI BD] + Salbutamol 200 mcg DPI SOS	FDC of [Formoterol 6 mcg + Budesonide 400 mcg DPI BD] + Montelukast 10 mg oral OD + Salbutamol 200 mcg DPI SOS

DPI - Dry powder inhalation, OD - Once a day, BD - Twice a day, SOS - As and when required

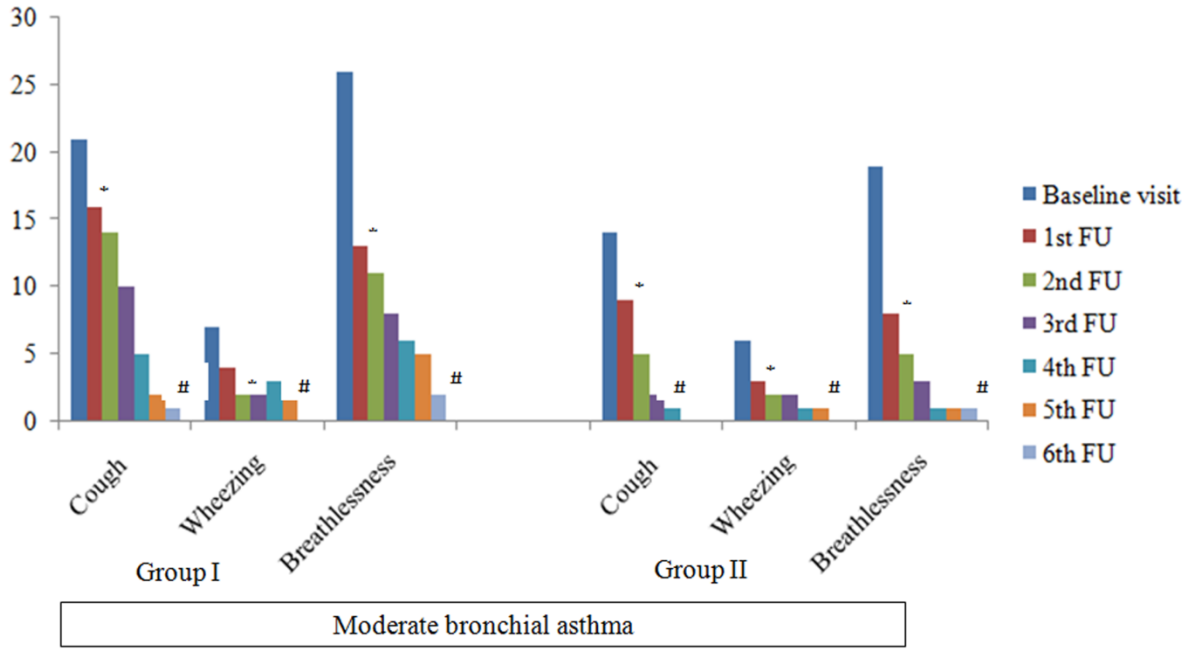

Figure 2: Clinical symptoms of patients in moderate bronchial asthma at different time interval.
Values are expressed as absolute numbers, FU - Follow up, * p<0.05 as compared to baseline, # p<0.05 as compared to 3rd FU.

Table 2: Clinical symptoms of patients at the time of enrolment.

Clinical symptoms	Group I (*n* = 26)	Group II (*n* = 19)
Cough (%)	21 (81)	14 (74)
Wheezing (%)	7 (27)	6 (32)
Breathlessness (%)	26 (100)	19 (100)

Values are expressed as absolute numbers and percentage in parentheses.

Table 3: Nocturnal awakening and frequency of inhaled short acting β_2-agonist at the time of enrolment.

Clinical symptoms	Group I (*n* = 26)	Group II (*n* = 19)
No. of nocturnal awakening (per month)	6.7 ± 1.1	6.6 ± 0.9
Frequency of inhaled short acting β_2-agonist (per month)	46.7 ± 6.8	53.6 ± 7.2

Values are expressed as mean ± SD

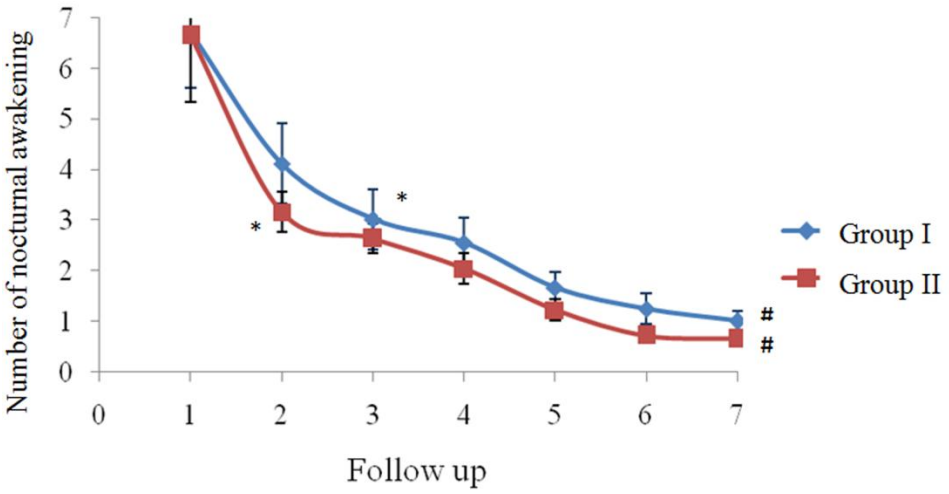

Figure 3: Comparison of number of nocturnal awakening per month in patients of moderate bronchial asthma at different time interval (mean ± SD).
FU - Follow up * $p<0.05$ as compared to baseline, # $p<0.05$ as compared to 3rd FU.

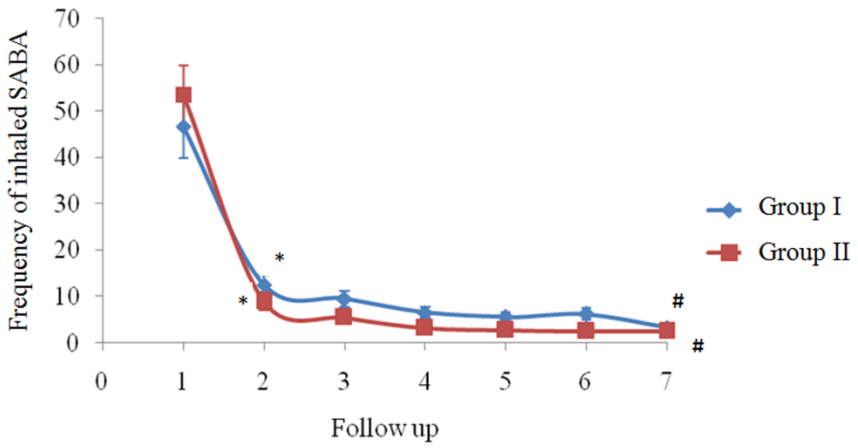

Figure 4: Comparison of frequency of inhaled short acting β_2-agonist per month in patients of moderate bronchial asthma at different time interval (mean ± SD).
FU - Follow up, SABA - short acting β_2-agonist, * $p<0.05$ as compared to baseline, # $p<0.05$ as compared to 3rd FU.

Table 4: Base line pulmonary function tests of patients with mild and moderate bronchial asthma.

PFTs	Normal Values (as per height and weight)	Group I (*n* = 26)	Group II (*n* = 19)
FEV_1 (Liter)	3.6 ± 0.7	2.3 ± 0.2*	2.2 ± 0.2*
FVC (Liter)	4.3 ± 0.9	4.1 ± 0.3	4.1 ± 0.3
PEF (liter/sec.)	8.5 ± 1.4	5.6 ± 0.5*	5.3 ± 0.4*
$FEV_{25-75\%}$ (liter/sec.)	3.9 ± 0.6	2.6 ± 0.2*	2.5 ± 0.2*
$FEV_{1\%}$	85.9 ± 2.6	57.4± 3.3*	53.9 ± 2.9*

Values are expressed as mean ± SD, PFTs - Pulmonary function tests, FVC - Forced vital capacity, FEV_1 - Forced expiratory volume in 1 second, PEF - Peak expiratory flow, $FEV_{25-75\%}$ - Forced expiratory flow 25-75%, $FEV_{1\%}$ - Forced expiratory volume 1%, * p<0.05 as compared to normal values.

Table 5: Comparison of clinical symptoms of patients at different time interval.

Group	Clinical symptoms	Baseline	1st FU	2nd FU	3rd FU	4th FU	5th FU	6th FU
I (*n*=26)	Cough (%)	21(81)	16(61)*	14(54)	10(79)	5(19)	2(08)	1(04)**
	Wheezing (%)	7(27)	4(15)	2(08)*	2(08)	3(12)	2(08)	0(0)**
	Breathlessness (%)	26(100)	13(50)*	11(42)	8(31)	6(23)	5(19)	2(08)**
II (*n*=19)	Cough (%)	14(74)	9(47)*	5(26)	2(11)	1(5)	0(0)	0(0)**
	Wheezing (%)	6(32)	3(16)*	2(11)	2(11)	1(5)	1(5)	0(0)**
	Breathlessness (%)	19(100)	8(42)*	5(26)	3(16)	1(5)	1(5)	1(5)**

Values are absolute count (%), FU - Follow up * p<0.05 as compared to baseline, ** p<0.05 as compared to 3rd FU.

Table 6: Comparison of nocturnal awakening and frequency of inhaled short acting β_2-agonist per month of patients in each group at different time interval.

Groups	Clinical symptoms (per month)	Baseline	1st FU	2nd FU	3rd FU	4th FU	5th FU	6th FU
I	No. of nocturnal awakening	6.7 ± 1.1	4.1 ±0.8	3.0±0.6*	2.6 ± 0.5	1.7±0.3	1.3±0.3	1.0±0.2**
	Frequency of inhaled SABA	46.7 ±6.8	12.5±2.1*	9.5 ±1.7	6.6 ±1.2	5.4±1.1	6.2±1.3	3.3±0.5**
II	No. of nocturnal awakening	6.7 ± 1.3	3.2 ± 0.4*	2.6 ±0.3	2.0 ±0.3	1.2±0.2	0.7±0.1	0.7±0.1**
	Frequency of inhaled SABA	53.6 ± 6.3	8.9 ±2.0*	5.4 ± 1.5	3.2 ±0.8	2.7±0.7	2.5±0.6	2.5±0.5**

Values are expressed as mean ± SD, FU - Follow up, SABA - Short acting β_2-agonist, * p<0.05 as compared to baseline, ** p<0.05 as compared to 3rd FU

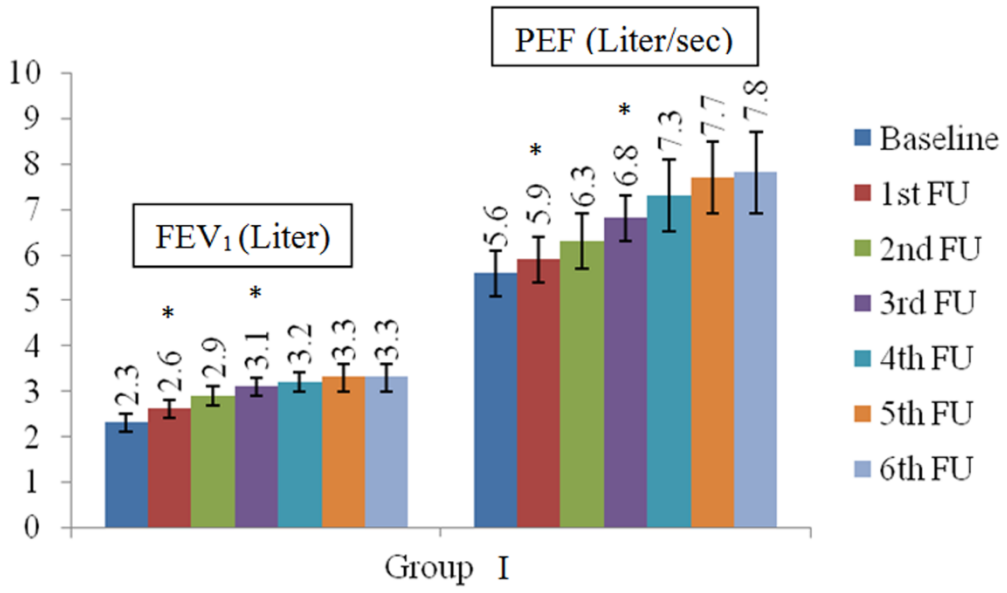

Figure 5: Comparison of FEV_1 and PEF of moderate bronchial asthma patients treated with LABA + ICS at different time interval (*n*=26).

Values are in mean ± SD, FU - Follow up, LABA - Long acting β2-agonist, ICS - Inhaled corticosteroids, FEV_1 - Forced expiratory volume in 1 second, PEF - Peak expiratory flow, * $p<0.05$ as compared to baseline.

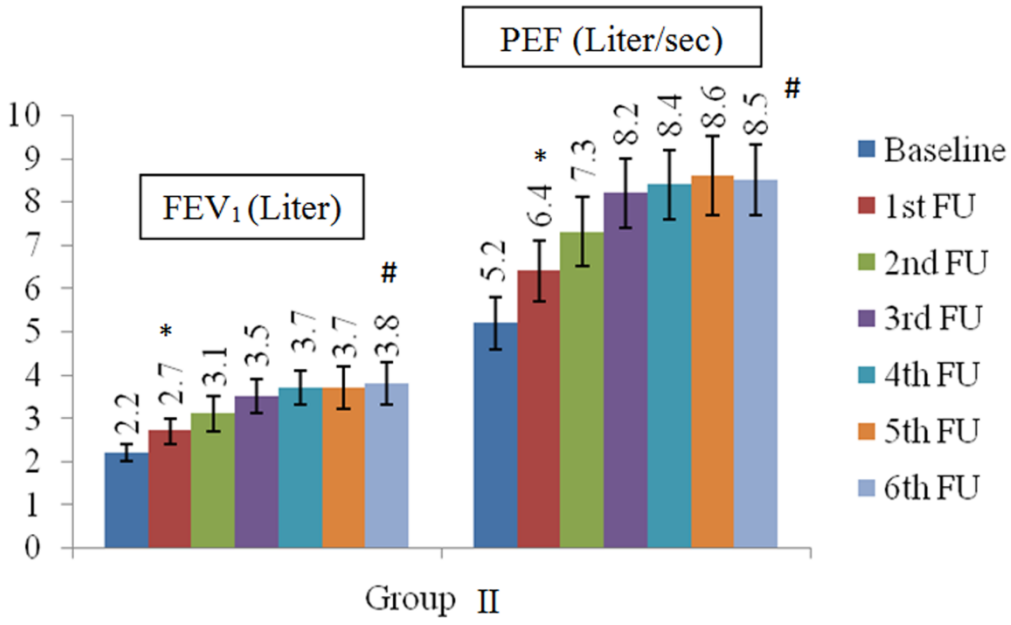

Figure 6: Comparison of FEV_1 and PEF of moderate bronchial asthma patients treated with LABA + ICS + montelukast at different time interval (*n*=19).

Values are in mean ± SD, FU - Follow up, LABA - Long acting β2-agonist, ICS - Inhaled corticosteroids, FEV_1 - Forced expiratory volume in 1 second, PEF - Peak expiratory flow, * $p<0.05$ as compared to baseline, # $p<0.05$ as compared to 3rd FU.

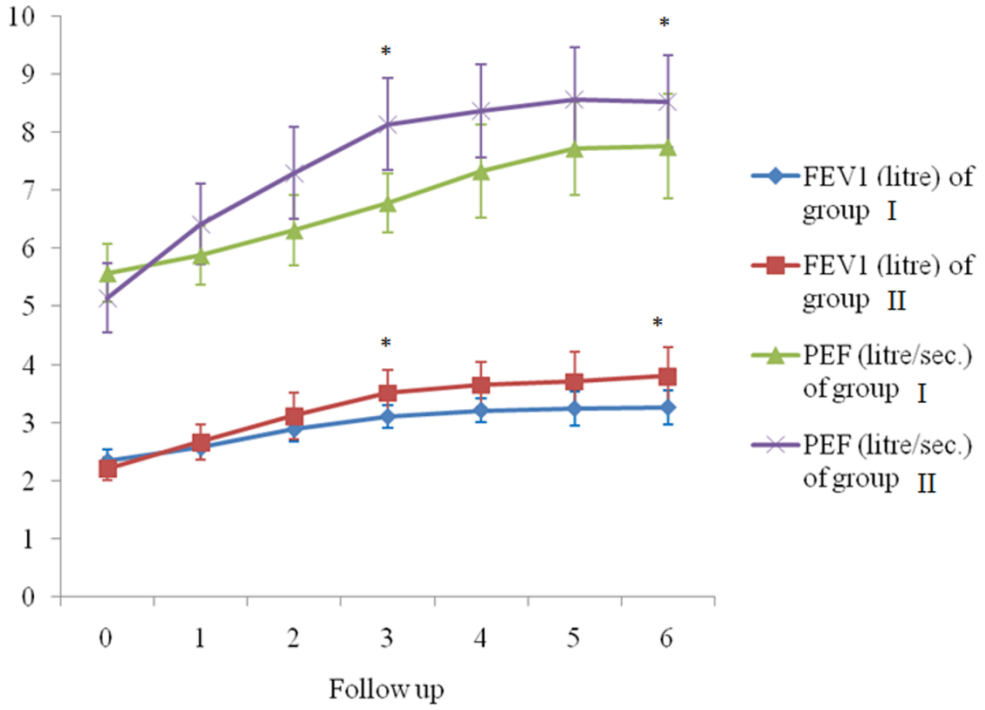

Figure 7: Comparison of FEV1 and PEF in moderate asthma patients treated with LABA + ICS with or without montelukast at different time interval.

Values are in mean ± SD, FU - Follow up, FEV_1 - Forced expiratory volume in 1 second, PEF - Peak expiratory flow, LABA - Long acting β2-agonist, ICS - Inhaled corticosteroids, * p<0.05 as compared to group I.

Table 7: Comparison of pulmonary function tests of patients with bronchial asthma at different time interval.

Groups	Parameter	Baseline	1st FU	2nd FU	3rd FU	4th FU	5th FU	6th FU
I								
	FEV_1(Liter)	2.3 ± 0.2	2.6 ± 0.2*	2.9 ± 0.2	3.1 ± 0.2*	3.2 ± 0.2	3.3 ± 0.3	3.3 ± 0.3
	FVC (Liter)	4.1 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3
	PEF (liter/sec.)	5.6 ± 0.5	5.9 ± 0.5*	6.3 ± 0.6	7.2 ± 0.6*	7.2 ± 0.8	7.1 ± 0.8	7.3 ± 0.9
	$FEV_{25-75\%}$ (lit/sec.)	2.6 ± 0.2	2.8 ± 0.2*	2.9 ± 0.3	3.1 ± 0.3*	3.4 ± 0.2	3.6 ± 0.2	3.6 ± 0.3
	$FEV_{1\%}$	57.4±3.3	62.2±3.8*	68.7±4.9	74.0±4.8*	75.4±5.1	75.6±4.8	76.2±5.2
II								
	FEV_1 (Liter)	2.2± 0.2	2.6±0.3*	3.1± 0.4	3.5 ± 0.4	3.7 ± 0.4	3.7 ± 0.5	3.8±0.5**
	FVC (Liter)	4.1± 0.3	4.2 ± 0.3	4.3 ±0.3	4.4 ± 0.3	4.4 ± 0.3	4.5 ± 0.3	4.5 ± 0.3
	PEF (liter/sec.)	5.1± 0.6	6.4±0.7*	7.3 ±0.8	8.1 ± 0.8	8.4 ± 0.8	8.5 ± 0.9	8.5±0.8**
	$FEV_{25-75\%}$ (lit/sec.)	2.5 ±0.3	2.9 ± 0.2*	3.3 ±0.3	3.9 ± 0.3	4.0 ± 0.4	4.1 ± 0.4	4.1±0.4**
	$FEV_{1\%}$	53.9±3.4	63.4±4.1*	72.7±5.6	80.6 ± 6.1	83.2±5.9	83.6±5.8	84.5±6.0**

Values are in Mean ± SD, FU - Follow up. FVC - Forced vital capacity, FEV_1 - Forced expiratory volume in 1 second, PEF – Peak expiratory flow, FEV_{25-75} - Forced expiratory flow 25-75%, $FEV_{1\%}$ - Forced expiratory volume 1%, * p<0.05 as compared to baseline values ** p<0.05 as compared to 3rd FU.

Table 8: Comparison of clinical symptoms and pulmonary function tests of patients with moderate bronchial asthma.

Visit / Parameter	Baseline		3rd FU		6th FU	
	Group I (*n* = 26)	Group II (*n* = 19)	Group I (*n* = 26)	Group II (*n* = 19)	Group I (*n* = 26)	Group II (*n* = 19)
Cough (%)	21(81)	14(74)	10(79)	2(11)*	1(04)	0(0)
Wheezing (%)	7(27)	6(32)	2(08)	2(11)	0(0)	0(0)
Breathlessness (%)	26(100)	19(100)	8(31)	3(16)*	2(08)	1(5)
Mean no. of nocturnal awakening / month	6.7 ± 1.1	6.7 ± 1.3	2.6 ± 0.5	2.0 ± 0.3	1.0 ± 0.2	0.7 ±0.1
Mean frequency of inhaled SABA	46.7 ± 6.8	53.6 ± 6.3	6.6 ± 1.2	3.2± 0.8*	3.3 ± 0.5	2.5 ± 0.5**
Mean FEV_1 (Liter)	2.3 ± 0.2	2.21 ± 0.2	3.1 ± 0.2	3.52±0.4*	3.3 ± 0.3	3.81±0.5**
Mean PEF (liter/sec.)	5.6 ± 0.5	5.15 ± 0.6	7.2 ± 0.6	8.15±0.8*	7.3 ± 0.9	8.54±0.8**

FU - Follow up, FVC - Forced vital capacity, FEV_1 - Forced expiratory volume in 1 second, SABA - short action β_2-agonist, * $p<0.05$ as compared to group I at 3rd FU ** $p<0.05$ as compared to group I at 6th FU.

Pulmonary function tests (PFTs):
A significant improvement ($p<0.05$) in FEV_1, PEF, $FEV_{25-75\%}$ and $FEV_{1\%}$ was observed in both groups at first follow up as compared to baseline data (Table 7). Further, the maximum improvement in FEV_1, PEF, $FEV_{25-75\%}$ and $FEV_{1\%}$ was observed up to third follow up in group I. However, FEV_1, PEF, $FEV_{25-75\%}$ and $FEV_{1\%}$ continued to improve significantly ($p<0.05$) till the end of study in group II. No improvement was observed in FVC in any of groups. The details are shown in table 7 and figure 5, 6.

Comparison between groups

The general characteristic and clinical symptoms of patients in group I and II was comparable at the time of enrollment. A comparison between group I and II at the time of 3rd follow-up showed significant difference ($p<0.05$) in breathlessness, cough, frequency of inhaled short acting β_2-agonist per month, FEV_1 and PEF. However, no significant difference in wheezing and number of nocturnal awakening per month was observed between group I and group II at third follow up. In addition, there was significant difference ($p<0.05$) in frequency of inhaled short acting β_2-agonist per month, FEV_1 and PEF in group II as compared to group I at 6th follow up. The details are shown in table 8 and figure 7.

DISCUSSION

During the past 40 years, major advances have been made in the prevention, diagnosis, and treatment of lung diseases. Death rates from lung diseases have been declined significantly, and people live longer.[7] Yet, despite tremendous progress, morbid lung diseases especially bronchial asthma continues to impose a significant clinical, social and economic burden on patients and the national health care system. According to World Health Organization estimates 300 million people suffer from bronchial asthma.[8]

Our study observed that more number of male patients as compared to females in moderate asthma category was observed in our study. This can probably because male members remain more mobile (due to work or otherwise) and thus are exposed to dust, allergen and air pollution. Secondly, they are main earning member of the family in India, can not afford to lose their daily wages and therefore ensure medical treatment by frequent visits to hospital. Majority of the patients in our study belonged to lower income class and lower middle class. This is expected at a Government hospital where bulk of the services provided is free of cost and most of the patients are from rural part of Gujarat, Rajasthan and Madhya Pradesh. Mean height of patients in our study was comparable with mean height reported in national family health survey conducted in Indian population.[9]

Clinical presentation and pulmonary function tests at baseline

The clinical hallmark of asthma symptoms i.e. breathlessness, coughing and wheezing was observed in

both category of patients. Breathlessness was observed in all patients. This can be because of bronchoconstriction; however, airway edema, vascular congestion, and luminal occlusion with exudate also contribute to a great extent. A randomised controlled clinical trial conducted in UK[10] also observed similar symptoms. Nocturnal awakening is one of the cardinal symptoms of bronchial asthma and was also observed in our study in moderate asthma patients. A study conducted in USA also showed that nocturnal awakening occurred in one third of the patients with moderate asthma.[11]

The clinical asthma was also corroborated by suggestive changes in pulmonary function tests especially FEV_1 and PEF. These tests are major determinants of mild, moderate and severe bronchial asthma and changes in FEV_1 is reflected on $FEV_{25-75\%}$ and $FEV_{1\%}$. The allotment of patients into moderate asthma category in our study is on similar lines reported by expert panel.[12]

Drug therapy and follow up

A rational approach to pharmacotherapy of bronchial asthma is to use 'relievers' such as bronchodilators and 'controllers' like anti-inflammatory agents.[13] Our study observed that patients with moderate bronchial asthma were treated with long acting β_2-agonist plus glucocorticoids either alone or in combination of montelukast. A dramatic improvement in clinical symptomatology especially cough and breathlessness, frequency of nocturnal awakening and inhaled SABA was observed in patients of moderate bronchial asthma treated with combination of LABA + ICS + montelukast at first follow up (8 weeks). Our observations are consistent with the studies conducted by Ducharme FM (2004).[14] Improvement in clinical symptomatology of moderate bronchial asthma was remarkable due to additive effect of montelukast to fixed dose combination (FDC) of corticosteroids plus long acting β_2-agonist. This can be partly explained by the fact that patients of moderate bronchial asthma treated with ICS + LABA alone, a delayed improvement in wheezing and nocturnal awakening was seen at second follow up. In case of moderate bronchial asthma, alone short acting β_2-agonist is not sufficient to decrease clinical symptoms**.** A meta-analysis has reported inhaled corticosteroids exhibit a relatively shallow dose-response curve for anti-inflammatory efficacy.[15] Treatment with corticosteroids appears to have a limited impact on airway inflammation and leukotriene levels. It showed that many patients receiving inhaled corticosteroids continue to experience bronchial asthma symptoms, possibly because corticosteroids do not completely inhibit the synthesis and release of leukotrienes in the lungs. The leukotrienes LTC4, LTD4, and LTE4 induce many of the pathophysiological changes in the lungs of patients with bronchial asthma, including airflow obstruction, mucus secretion, reduced mucociliary clearance and inflammatory cell infiltration. Montelukast being specific against leukotrienes, patients showed significant early response in wheezing and number of nocturnal awakening. It has been reported that montelukast also reduce airway eosinophilic inflammation in patients with chronic bronchial asthma. It was interesting to note that clinical symptoms in patients of moderate bronchial asthma continued to improve till the end of study. This can be explained by the fact that airway inflammation is an essential component in moderate bronchial asthma requiring anti-inflammatory glucocorticoids and leukotriene antagonists for symptom control and to improve lung functions. The progressive improvement in clinical asthma and lung functions could be due to continuous decrease in airway inflammation by combine treatment of montelukast, corticosteroids and long acting β_2- agonist.

A parallel improvement in pulmonary function test was also noted in our study. We observed that there was significant ($p<0.05$) improvement in FEV_1 and PEF in all patients following drug treatment at first follow up. Improvement in FEV_1 and PEF was observed by addition of montelukast in moderate bronchial asthma patients treated with LABA + ICS + montelukast. There was continuous, progressive, significant improvement in lung functions till the end of the study. Similar observations have been reported by Vaquerizo MJ.[15] The persistent improvement in lung functions in montelukast treated patients explains the role of proinflammatory mediator leukotriene giving rise to bronchoconstriction and smooth muscle hypertrophy.[10] Thus treatment with montelukast has better control over PFTs for longer period of time. While inhaled corticosteroids affect a variety of inflammatory pathways in bronchial asthma but are not specific for leukotrienes. Therefore combination therapy of montelukast and ICS is more effective to improve pulmonary function tests.

Strength and limitations of the study

We had undertaken a prospective study over a period of 24 months wherein all the information was recorded precisely. The strength of our study includes long term follow up (48 weeks) of each patient. Secondly, the patients were observed for clinical symptoms (subjective assessment) which were corroborated with objective test (pulmonary function tests). In order to find out the actual effect of test drugs we enrolled newly diagnosed asthma patients who were not exposed to bronchodilators or corticosteroids earlier.

However, like any other study, there were certain limitations. For example, it was an open-label observational study conducted at single center. The decision to prescribe montelukast to asthma patients was on the discretion of treating physician and willingness and affordability of the patient to purchase the drug. A narrow and restricted patient eligibility criteria, as in other clinical trial, the study may have selected a specific group of asthma patients.

Despite these limitations, we believe that the data generated in our study leads to certain important conclusions. For example, addition of montelukast to long acting β_2-agonist plus corticosteroids in moderate bronchial asthma provides significant additional asthma control by improving lung functions especially FEV_1 and PEF and reducing the use of rescue short acting β_2-agonist. In patients with mild bronchial asthma, the clinical effect of short acting β_2-agonist was so profound that the advantage gained by addition of montelukast was not evident.

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