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ORIGINAL ARTICLE

ROLE OF ORAL MONTELUKAST IN ACUTE ASTHMA EXACERBATIONS: A RANDOMIZED PLACEBO CONTROLLED TRIAL

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ABSTRACT: BACKGROUND: Leukotriene receptor antagonists (LTRAs) are well established in the management of outpatient asthma. However, there is very little information as to their role in acute asthma exacerbations. The present study was done to evaluate the clinical efficacy of oral Montelukast as an add on therapy to the usual standard therapy of acute attack of bronchial asthma. **MATERIALS AND METHODS:** A randomized single blinded controlled study was conducted in a tertiary care teaching hospital. A total of 320 patients with age >18 years of acute exacerbations due to bronchial asthma were included in the study. The patients were randomized into two study and control groups. The study group patients received oral Montelukast (10mg) once daily for 2 weeks, while the control group received a placebo. All the patients received standard therapy according to GINA guidelines. Improvements in lung function tests, clinical symptoms and relapse rates were monitored at baseline, at discharge and at 2 weeks. Side effects profile was also monitored. **RESULTS:** A total of 255 patients were finally assessed. One hundred thirty patients belonged to study group and 125 in the control group. Baseline characteristics were similar and well matched in both the groups. Mean age was 39.9±15.8 years in study group and 42.8±12.8 in the control group and majority were female patients in both the groups. At the end of 2 weeks, it was observed that there were no significant improvements in FEV_1 and FVC as compared to the control group. However, there was significant improvement in PEFR at 2 weeks (0.4 L/sec, 12%) as compared to the control group ($p < 0.0376$). Length of hospital stay was similar in both the groups. No serious adverse effects were noted during the course of the study. **CONCLUSIONS:** In acute asthma exacerbations, the present study showed that additional administration of oral Montelukast resulted in significantly higher PEFR at 2 weeks as compared to the standard treatment alone. These findings should be confirmed by conducting a larger population based clinical study.

KEYWORDS: Bronchial asthma, acute asthma, leukotriene receptor antagonist, Montelukast, FEV_1, PEFR.

INTRODUCTION: Acute asthma consistently ranks among the most frequent causes of emergency department visits in children and adults and is a major contributor to time away from work, with an estimated two-million emergency department visits with 500,000 hospital admissions annually in United States.[1] Furthermore, acute asthma may account for a disproportionate share of direct asthma costs; in one study of asthma resource use, accounted for 3.8% of total asthma encounters, but they comprised 44.6% of asthma costs.[2] Treatment goals for acute asthma include correction of significant hypoxemia, and reduction of likelihood of significant reversal of airflow obstruction. Currently accepted initial therapy includes oxygen and short-acting $beta_2$-agonist broncho-dilators; in addition, systemic corticosteroids should be considered for those patients who are severely ill at presentation or who fail to respond to initial measures. However, up to 30% of patients who present with acute

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asthma will fail to respond adequately to short-acting beta$_2$ agonists,[3] and benefit from systemic corticosteroids is not generally observed for 4–6 hours or longer.[4] As a result, current therapeutic options for acute asthma do not adequately address treatment goals for a substantial number of patients.

Montelukast is a leukotriene receptor (CysLT1) antagonist when administered orally is effective in the management of chronic asthma.[5] Given as a single intravenous bolus**.** infusion to patients with chronic asthma, montelukast causes significant benefit (Measured as change in FEV1 from baseline) within 15 minutes, and this effect is sustained for at least 24 hours.[6] They may also provide benefit, additional to that achieved by current treatment, in acute attack.[7] They have been shown to have acute bronchodilator effect which may be of additional help in acute attack of bronchial asthma. There is very limited literature regarding the use of leukotriene antagonists in acute attack of bronchial asthma.[8] In our study, we tested the hypothesis that treatment with a leukotriene receptor antagonist (LTRA), montelukast sodium would improve airway obstruction and clinical outcomes in acute asthma exacerbation and would subsequently decrease the duration of hospital stay.

MATERIALS AND METHODS: The prospective study was carried out in a tertiary care KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum in the department of Pulmonary Medicine, during the period of January 2013 – December 2014.

Study Subjects: All patients of age 16 and above who presented with acute asthma exacerbation were screened for enrollment in the study. Informed consent was obtained. The eligibility criteria included a diagnosis of acute asthma exacerbation that required hospitalization as defined by the Global Initiative for National Asthma (GINA) Guidelines.[9] The criteria for hospitalization was FEV1 <70% predicted or PEF <300L/min after 30 -minutes of receiving initial treatment in the ER, respiratory rate >24 breaths/min and no improvement in symptoms such as shortness of breath or wheezing. The patients with following conditions were excluded from the study: lifetime smoking history >10 pack years, pregnant female patients or breast feeding or unable to take adequate contraceptive precautions, patients already on LTRA, phenytoin, rifampicin, phenobarbitone, ischaemic heart disease with left ventricular failure, HIV positive patients and children <18 years.

Study Design: This was a randomized, single-blind, placebo controlled parallel group drug trial conducted over a period of two years from January 2013 to December 2014. All patients presenting either to the emergency department or outpatient clinics of the hospital with acute asthma exacerbation were screened for inclusion in the study. The patients with mild and moderate severity of asthma exacerbations were included in the study. Patients with severe exacerbations were excluded. Post-bronchodilator spirometry after salbutamol nebulisation 2.5mg was performed in all the patients to exclude COPD patients and to establish diagnosis of bronchial asthma. A written informed consent was obtained before enrollment and findings were shared with subjects interested in the study outcome on clinic follow-up. The patients underwent a baseline spirometry and peak expiratory flow (PEF) testing soon after enrollment. A brief questionnaire was used to obtain information about the duration, severity and treatment of asthma. A questionnaire concerning baseline characteristics including age, gender, height, weight, BMI, presenting symptoms, past history and duration of asthma, current medications, history of smoking, presence of co-morbidities –

diabetes, hypertension, ischaemic heart disease, previous history of admissions and chest X-ray findings were recorded. The study was approved by the Institutional Ethical Committee.

Measurements: The selected patients were briefed about the study and written informed consent was obtained. The study was done as a randomized single blinded controlled study. A questionnaire concerning baseline characteristics including age, gender, height, weight, BMI, presenting symptoms, past history and duration of asthma, current medications, history of smoking, presence of co-morbidities–diabetes, hypertension, ischaemic heart disease, previous history of admissions and chest X-ray findings were recorded. All patients with a diagnosis of mild and moderate exacerbations were included in the study. Pulmonary function tests were done on admission using COPD -6 Vitalograph Spirometer (Model 4000, Vitalograph, Ennis, Ireland). The parameters that were included for assessment included FEV_1, FVC, FEV_1/FVC ratio and PEFR. After initial assessment, all the patients were then randomized in 1: 1 ratio in either study or control groups by a computer generated method. Patients in study group received 10mg of oral Montelukast and the control group received placebo.

This study was done single blinded with the help of clinical pharmacist. All the patients in both the groups received standard treatment for management of acute attack of bronchial asthma as per the GINA guidelines. These included parenteral steroids, short acting $beta_2$ agonists with inhaled anticholinergics by nebulisation every 4-6 hourly depending upon severity, intravenous theophylline derivatives, oxygen therapy and other supportive therapy. Antibiotics were prescribed only if there was suspicion of infection. The spirometry was done on admission, at discharge, at 2 weeks and at 4 weeks. After the end of the study, the detailed clinical evaluation was carried out with spirometric evaluation with COPD-6 Vitalograph, any adverse effects due to the drug and number of exacerbations was noted for all the patients. Thus, the global assessment was done for all the patients at the end of 4 weeks of therapy.

Outcome Assessment: The primary outcomes of the study were a) improvement in lung function measured as FEV_1, FVC and PEF over the course of hospital stay and discharge and b) relapse rates for one month. Secondary outcome included development of side effects and complications such as respiratory failure, cardiac arrest and/or death.

Statistical Analysis: For descriptive analysis mean±standard deviation are reported for continuous variables, and number (%) for categorical variables. In univariate analyses, differences in proportions for type of treatment groups were assessed by using the Chi-square test or Fisher exact test where appropriate. For contrasts of continuous variables, independent sample t-test was used to assess the difference of means. All analyses were conducted by using the Statistical package for social science (SPSS Release 15.0, standard version, copyright © SPSS; 1989–02), p-values were two sided and considered as statistically significant if <0.05.

RESULTS: A total of 320 patients were initially included in the study. Twenty patients were withdrew the consent before randomization. Thus, 300 patients were randomized in two groups equally. Twenty patients in study group and twenty five patients in control group were lost to follow up. Thus, a final analysis was done for 255 patients-130 patients belonged to study group and 125 patients belonged to control group (Fig. 1).

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Baseline characteristics of the patients in the two groups were identical (Table 1). Dyspnea, chest tightness and coughing were the most common presenting symptoms in the patients presenting with acute attack of bronchial asthma. Fever was observed in more than one fourth of the patients in the present study (27.5%). Diabetes mellitus and hypertension were the most common co-morbid conditions. In the present study, it was observed that almost half of the patients had moderate severity of acute attacks of bronchial asthma while the remaining half had mild severity of acute attacks. Weather change was the major precipitating factor of the acute asthma attack in 43.1% of the patients followed by infection of the respiratory tract in 35.7% patients while 77 patients had a positive family history for asthma. The majority of patients were ex-smokers, 46.7% had a prior history of an acute exacerbation, with many patients having more than one admission in the previous year.

Primary Outcome Measures: In the present study, it was observed that improvement in FEV_1 at discharge and at 2 weeks was almost similar in both the groups (p=0.23) (Table 2). Similarly, it is observed that there was no improvement in FVC among the study and control group at any given point of treatment till 2 weeks of therapy. As far as PEFR is concerned, it was observed that there was significant improvement in PEFR at 2 weeks in the study group as compared to the control group (3.31±1.53l/sec vs 2.91±1.24l/sec) (p<0.0376). On further analysis, it was observed that there was statistically significant improvement in PEFR mean values in the study group from the baseline to 2 weeks in the Montelukast group as compared to the control group (p<0.0074) (Table 3). There was no significant variation in the duration of hospital stay between both the groups with the mean duration for patients belonging to Montelukast and placebo groups being 3.6±1.8 days and 3.7±2.1 days, respectively (p=0.90).

Secondary Outcome Measures: No patient in either group was withdrawn due to worsening asthma or adverse drug effect from the study. Table 4 demonstrates the various adverse events observed in the present study. These were mild and transient in nature and included headache, muscle cramps and skin rashes. There was no statistical difference between the two groups (p<0.35).

DISCUSSION: Our study did not reveal significant differences in pulmonary function tests measured as FEV_1, and FVC at admission, at discharge and at 2 weeks in patients with mild and moderate acute asthma exacerbation that were given oral montelukast vs. placebo. But there was significant improvement in PEFR at 2 weeks of therapy with oral Montelukast as compared to placebo. The efficacy and tolerability profile of oral montelukast were comparable to placebo and no serious adverse effects were encountered.

The pathology of asthma triggers the arachnoid acid cascade leading to formation of leukotrienes via the 5-lipoxygenase pathway. The cysteinyl leukotrienes possess pro-inflammatory characteristics which can directly cause or potentiate airflow obstruction by increased mucosal secretion and bronchospasm.[10] Leukotriene pathway modifiers, hence, are a subject of interest as a possible adjunct therapy in the acute management of asthma exacerbation. The mean improvement in FEV_1 in the present study was observed to be 21% in the Montelukast group as compared to the placebo at the end of 2 weeks. Camargo et al.,[11] randomized 201 patients to three groups with two receiving separate doses of montelukast (7mg and 14mg) and one group receiving placebo. They reported significantly higher FEV1 in patients receiving standard therapy with montelukast as

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compared to placebo at 10 minutes (p=0.03), 20 minutes (p=0.007) and two hours (p=0.003). These results were validated in a more recent study in Japan which reported both IV monteleukast 7mg and 14mg to be effective as an adjunct therapy over 60 minutes; p <0.05 and p <0.001 respectively.[12] A study by Silverman et al.,[13] evaluated the effects of another LTRA, zafirlukast. They randomized patients into three groups; oral zafirlukast at 20mg and 160mg vs. placebo. They looked at the time to relapse in the outpatient setting after discharge from the emergency department and found reduction in the absolute rate of relapse by 5.3% in patients treated with zafirlukast. They reported significant improvement in FEV1 and dyspnea in the ER only with 160mg of zafirlukast.

Similarly, Ramsay et al.,[14] randomized 73 patients and found a significantly higher peak expiratory flows (PEFs) measured in the morning after admission in patients who received montelukast (p=0.046, 95% CI of 1.15- 113.6 L/min) as compared to placebo group. Gaddy et al.,[15] showed that intravenous leukotriene receptor antagonists could produce a 22% improvement in FEV_1 from baseline in those with stable asthma with a baseline FEV_1 of 50% - 80% predicted. However, a study by Zubairi et al.,[16] did not observe any significant differences in FEV_1 and PEFR at admission and discharge in patients hospitalized with acute asthma exacerbations that were given oral Montelukast versus placebo. Nelson et al.,[17] did not observed any improvement in FEV_1 among children aged 6–14years taking oral Montelukast in acute attack of asthma and concluded that oral Montelukast has got no role in the acute attack of bronchial asthma. Thus our results are similar to those other studies by Gaddy et al[15], Silverman et al[13] and Camargo et al.,[11]

In the present study, it was observed that there was no improvement in FVC among the study group patients taking oral Montelukast till 2 weeks of therapy. PEFR is the maximal flow achieved during maximally forced expiration initiated at full inspiration which is measured in liters/second or liters/minute. Our study showed there was significant improvement in PEFR at 2 weeks in the study group as compared to the control group (3.31±1.53l/sec vs 2.91±1.24l/sec; p<0.0376). Ramsay et al[14], in a randomized double blind placebo controlled study, has observed that patients who received Montelukast had a significantly higher PEFR values than those who received placebo the morning after admission with a difference of 57.4l/min (p<0.04).

In another study, Zubairi et al.,[16] had observed that there was no significant difference in PEFR during the hospital stay and at discharge with oral Montelukast therapy. Ferreira et al.,[18] observed that Montelukast group had shorter duration of hospital stay and better evolution of PEFR values (Median increase of 55% from baseline versus 44% in placebo group) but this did not reach statistical significance. In our study, diurnal PEFR variability could not be assessed as majority of the patients were illiterate and in spite of repeated request they did not record their readings on daily basis on two separate occasions in spite of providing the hand held mini-Wright peak flow meters.

In the present study, 14.6% in the study group and 12.0% in the control group developed adverse events which were mild and transient in nature and included headache, muscle cramps and skin rashes (p<0.35). Our study observed that during the follow up of 1 month period, there were 20 exacerbations (15.4%) in the study group while there were 28 exacerbations (22.4%) in the control group.

Although many asthma exacerbations are resolved promptly, a substantial proportion (Patients with moderate to severe exacerbations) will require prolonged therapy in an acute setting and/or hospitalization. For example, up to 30% of patients with acute asthma fail to respond adequately to short-acting β-agonists. Such patients typically receive systemic corticosteroids, but benefit from systemic corticosteroids is not generally observed for 4–6 hours or longer.[4]

Several studies have examined new interventions in acute asthma that could provide rapid and sustained relief from airflow obstruction, in addition to current standard treatment. For example, inhaled ipratropium may provide a modest bronchodilator benefit and an improvement in hospital admission rates, particularly in patients with severe asthma exacerbations.[19] Others have suggested, however, that there is little added benefit of ipratropium above that of standard therapy with β-agonists.[20] Moreover, anticholinergics do not appear to be effective for patients whose initial response to β-agonists is impaired, and at this point, there is no clear consensus regarding their use.[21] Other interventions for acute asthma that are current areas of active research include intravenous magnesium,[22] xanthines,[23] and inhaled helium/oxygen mixtures.[24] This study, if confirmed, suggests that montelukast may confer added benefit to current treatment options in the management of acute asthma.

The study has some limitations. Firstly, the sample size is relatively small. Secondly, the patients with severe exacerbations were excluded. Both these factors may have impacted on the strength of the difference observed in the two groups. Thirdly, the PEFR variability in both the groups could not be evaluated as patients failed to maintain the PEFR diary. Another limitation is the lack of biological surrogate markers like cysteinyl leukotriene levels which have shown to be higher in acute asthma exacerbations. It is possible that these levels may have been reduced in the patients but did not translate into clinical effectiveness yet.[25] Lastly, this was a single center and a single blinded study. Hence the results cannot be generalized to the whole population.

CONCLUSION: Our study suggests that there was additional benefit of using oral montelukast along with the standard therapy for the management of acute asthma exacerbation in mild to moderate acute exacerbations. We recommend that larger scale multicenter trials would better help to evaluate the role of cysteinyl leukotrienes antagonists in treating acute exacerbations of asthma.

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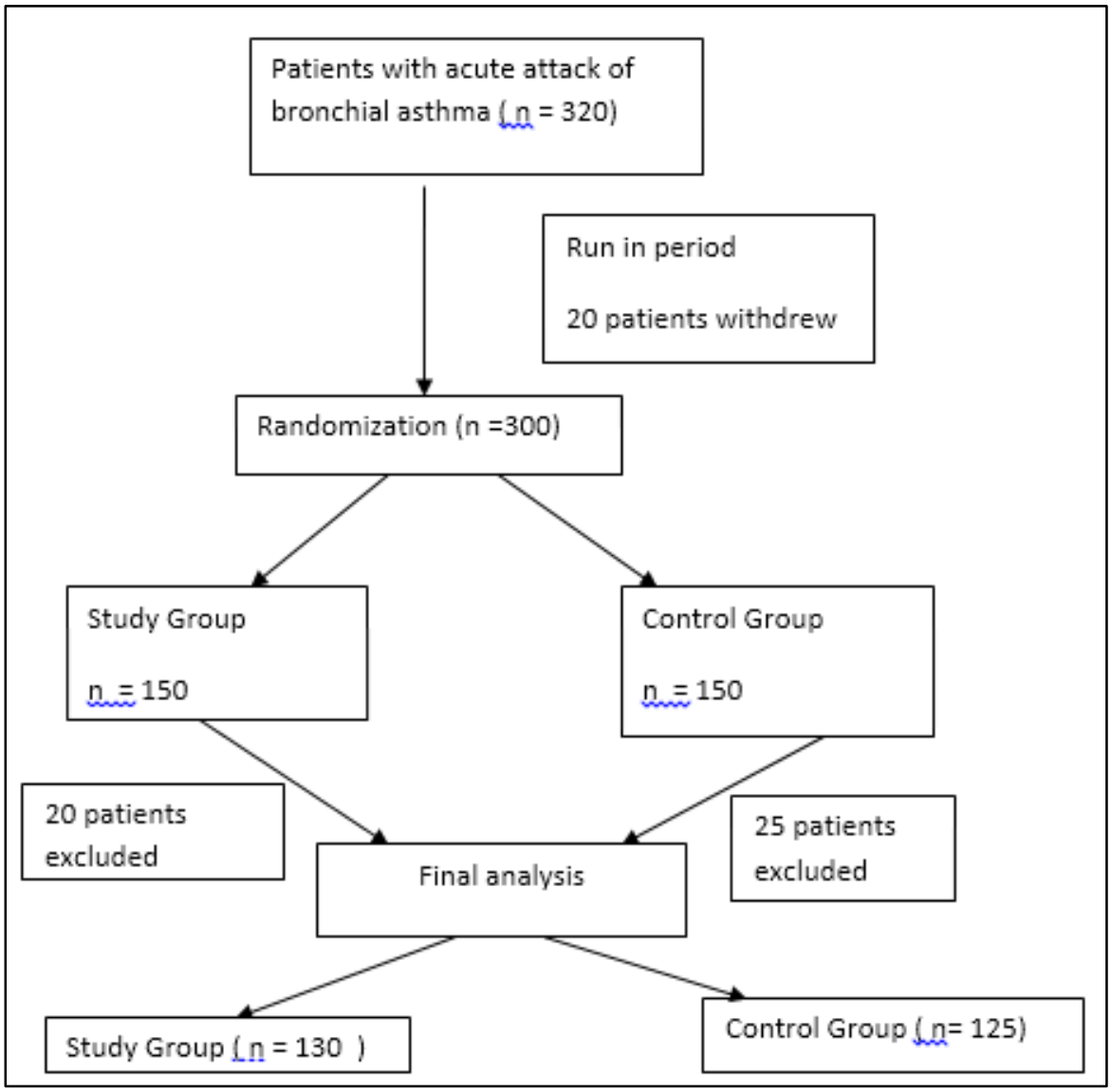

Fig. 1: Randomization Table

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Age Group (yrs)	Study Group No. (%)	Control Group No. (%)	p value
18-29	32(24.6)	29(23.2)	0.20
30-39	30(23.2)	34(27.2)	0.51
40-49	32(24.6)	27(21.6)	0.32
50-59	22(16.9)	23(18.4)	0.32
>60	14(10.7)	12(9.6)	0.30
Mean Age(yrs)	39.9±15.8	42.8±12.8	0.20
M: F Ratio	1: 1	1: 1	0.79
Duration of illness(yrs)	7.2±8.5	6.6±4.2	0.29
Mean BMI(kg/m2)	24.2±3.8	23.7±4.3	0.34
Co-morbidities	42(32.3)	38(30.4)	0.32
Mild exacerbation	68(52.3)	70(56.0)	0.34
Moderate exacerbation	62(47.7)	55(44.0)	0.34
Previous history of admissions in last 1 year	51(39.2)	58(46.4)	0.45
Precipitating Factors			
a) Infection	48(36.9)	43(34.4)	0.43
b) Weather changes	53(40.8)	57(45.6)	0.56
c) Non-compliance to drugs	67(51.5)	56(44.8)	0.21
d) Allergen exposure	41(31.5)	33(26.4)	0.35
f) None	13(10.0)	11(8.8)	0.23
Smoking status			
a) Non-smoker	22(16.9)	34(27.2)	0.50
b) Current smoker	46(35.4)	49(39.2)	0.30
c) Ex-smoker	62(47.7)	42(33.6)	0.61

Table 1: Baseline characteristics of the patients

Time Points	Study Group	Control Group	t-value	p-value
	Mean±Std. Dev.	Mean±Std. Dev.		
FEV_1				
On admission	1.15±0.60	1.24±0.72	-0.6206	0.5358
On discharge	1.41±0.71	1.52±0.73	-0.7263	0.4687
2 Weeks	1.72±0.71	1.66±0.71	1.1976	0.2329
FVC				
On admission	1.55±0.81	1.61±0.83	-0.6266	0.5318
On discharge	1.67±0.72	1.78±0.72	-1.4014	0.1631
2 Weeks	2.02±0.73	2.08±0.72	-0.3979	0.6912
PEFR				
On admission	2.22±1.34	1.93±1.22	1.5541	0.1222
On discharge	2.91±1.54	3.03±1.52	-0.1425	0.8868
2 Weeks	3.31±1.53	2.91±1.24	2.0973	0.0376

Table 2: Comparison of FEV_1, FVC and PEFR among study and control groups at different intervals of treatment

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Time Points	Study Group	Control Group	t-value	p-value
	Mean±SD	Mean±SD		
Difference from Admission – 2 Weeks				
FEV_1 improvement	0.78±0.68	0.37±0.55	4.0317	0.0001
FVC improvement	0.63±0.63	0.41±0.90	1.8623	0.0644
PEFR improvement	1.65±1.54	1.23±1.27	2.7147	0.0074
Difference from 1 Week -2 Weeks				
FEV_1 improvement	0.52±0.64	0.09±0.39	4.8845	0.00001
FVC improvement	0.51±0.62	0.20±0.65	3.0555	0.0026
PEFR improvement	0.93±1.40	-0.14±1.21	4.5931	0.00001

Table 3: Mean difference in FEV_1, FVC and PEFR values among study and control groups at differing intervals

Adverse Effects	Study Group No. (%)	Control Group No. (%)	p value
Headache	10(7.6)	8(6.4)	0.35
Muscle pain	7(5.3)	5(4.0)	
Rashes	2(1.5)	2(1.6)	
Total	19(14.6)	15(12.0)	

Table 4: Number of adverse effects in the study group during 1 month

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