Original Article

Effects of oral montelukast on airway function in acute asthma: A randomized trial

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ABSTRACT

Background: The role of leukotriene receptor antagonist is well known in the management of chronic asthma, but their efficacy in acute exacerbation of asthma is unknown. 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 162 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 (10 mg) 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, 1 week, 2 weeks, and 4 weeks. Side effects profile was also monitored. **Results:** A total of 160 patients were finally assessed. Seventy-eight patients belonged to study group and 82 in the control group. Baseline characteristics were similar and well matched in both groups. Mean age was 39.9 ± 15.8 years in the study group and 42.8 ± 12.8 in the control group and majority were female patients in both groups. At the end of 4 weeks, it was observed that the study group patients who received montelukast had better forced expiratory volume in 1 s (FEV_1) improvement by 21% (0.21 L) as compared to the control group ($P < 0.0033$). It was also observed that there was a better improvement in peak expiratory flow rate (PEFR) at 2 weeks (0.4 L/s, 12%) and at 4 weeks (0.9 L/s, 23%) as compared to the control group ($P < 0.0376$ and $P < 0.0003$ respectively). There was no difference in forced vital capacity (FVC), FEV_1/FVC ratio and relapse rates between the two groups. No serious adverse effects were observed during the study. **Conclusions:** In acute asthma exacerbations, the present study showed that additional administration of oral montelukast resulted in significantly higher FEV_1 at 4 weeks and PEFR at 2 weeks and 4 weeks as compared to the standard treatment alone. These findings should be confirmed by conducting a larger population-based clinical study.

KEY WORDS: Acute asthma, bronchial asthma, forced expiratory volume in 1 s, leukotriene receptor antagonist, montelukast, peak expiratory flow rate

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INTRODUCTION

Asthma is one of the most common chronic diseases globally with a rising incidence in developing countries. Asthma is a problem worldwide with an estimated 300 million affected individuals. The prevalence ranges from 1% to 18% in different countries.[1] Its incidence is on the rise all across the world, with bronchial asthma accounting for 4% of the pediatric outpatient visits.[2] 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 2-million emergency department visits and 500,000 hospital admissions annually.[3] Furthermore, acute asthma may account for a disproportionate share direct asthma costs; in one study of asthma resource use, hospitalizations accounted for 3.8% of total asthma encounters, but they comprised 44.6% of asthma costs.[4]

An acute attack of bronchial asthma is one of the most common reasons to visit the emergency department or a general practitioner. Mild asthma is defined as asthma that can be well controlled with low-intensity treatment such as low-dose inhaled glucocorticoids, leukotriene modifiers or cromones. Severe asthma is defined as asthma that requires high-intensity treatment to maintain good clinical control, or when symptoms are not controlled despite high-intensity treatment.[1] Standard treatments for acute asthma though effective, are inadequate for sustained improvement which includes parenteral steroids, inhaled beta$_2$ agonists and anticholinergics nebulization, intravenous theophyllines, and oxygen therapy. Leukotriene receptor antagonists (LTRAs) are a class of drugs which specifically act on leukotriene receptors, and they have an established role in the management of chronic asthma.[5] They may also provide benefit, additional to that achieved by current treatment, in an acute attack.[1] They have been shown to have acute bronchodilator effect which may be of additional help in an acute attack of bronchial asthma. There is very limited literature regarding the use of leukotriene antagonists in an acute attack of bronchial asthma.[6] Hence, the present study was done to evaluate the clinical efficacy of oral montelukast in an acute attack of bronchial asthma.

MATERIALS AND METHODS

The prospective study was carried out in the Department of Pulmonary Medicine, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum in bronchial asthma patients during January 2013 – June 2014.

Source of data
The data were collected from the patients who were diagnosed with an acute attack of bronchial asthma as per GINA guidelines in the Department of Pulmonary Medicine referred as both outpatients and inpatients, at KLE'S Dr. Prabhakar Kore Hospital and MRC, Belgaum. A total of 210 diagnosed cases of acute attack of bronchial asthma were initially included in the study.

Inclusion criteria
All patients aged above 18 years with a primary diagnosis of acute attack of bronchial asthma, under the care of a consultant chest physician, at KLE'S Dr. Prabhakar Kore Hospital and MRC, Belgaum were included in the study. The diagnosis was done based on clinical history and pulmonary function testing and staging done as per the GINA guidelines.

Exclusion criteria
Lifetime smoking history >10 pack years, pregnant female patients or breastfeeding or unable to take adequate contraceptive precautions, patients already on LTRA, phenytoin, rifampicin, phenobarbitone, ischemic heart disease with left ventricular failure, HIV positive patients and children <18 years.

Procedure
The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum. 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. Patients with bronchial asthma presenting in the acute attack were enrolled from emergency or outpatient clinics diagnosed and admitted by a consultant chest physician.

A questionnaire concerning baseline characteristics including age, gender, height, weight, body mass index (BMI), presenting symptoms, past history, and duration of asthma, current medications, history of smoking, presence of comorbidities – diabetes, hypertension, ischemic 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. Patients were categorized as mild, moderate, or severe exacerbations as per the GINA guidelines.[7] Patients with severe exacerbations were excluded from the study. Postbronchodilator spirometry after salbutamol nebulization 2.5 mg was performed in all the patients to exclude chronic obstructive pulmonary disease (COPD) patients and to establish the diagnosis of bronchial asthma.

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 forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC), FEV$_1$/FVC ratio, and peak expiratory flow rate (PEFR). After an 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 the study group received 10 mg 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 groups received standard treatment for the 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 nebulization every 4–6 hourly depending on severity, intravenous theophylline derivatives, oxygen therapy, and other supportive therapy. Antibiotics were prescribed only if there was suspicion of infection.

PEFR was recorded daily in the morning (around 8–10 a.m.) by Mini-Bell peak flow meter (Forumed SL, Spain) and continued every morning till the discharge or after 1 week. Lung function tests were repeated with the handheld spirometer (COPD-6 Vitalograph) at the time of discharge for

the inpatients and the outpatients returned for spirometric assessment after 1 week. All the patients were then followed up later at the outpatient department level, and assessment with spirometry was done at the end of 2 weeks. All the patients were followed up to 4 weeks after initiation of therapy, and this was the endpoint of the study. 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 were noted for all the patients. Thus, the global assessment was done for all the patients at the end of 4 weeks of therapy.

Statistical analysis

This is a randomized controlled study in which spirometric values were assessed and recorded till 1 month of follow-up. Comparison of age, BMI, and duration of the illness between both groups was done using student unpaired *t*-test. The presence of comorbidities and presentation of symptoms on admission were compared using Mann–Whitney U-test. Spirometric values such as FEV_1, FVC, FEV_1/FVC, and PEFR recorded at different points of time during the study were compared between the study and control groups using student unpaired *t*-tests. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 210 patients were initially included in the study. Twelve patients were withdrew the consent before randomization. Thus, 198 patients were randomized in two groups equally. Twenty-one patients in study group and 17 patients in control group were lost to follow-up. Thus, a final analysis was done for 160 patients - 78 patients belonged to study group and 82 patients belonged to control group [Figure 1].
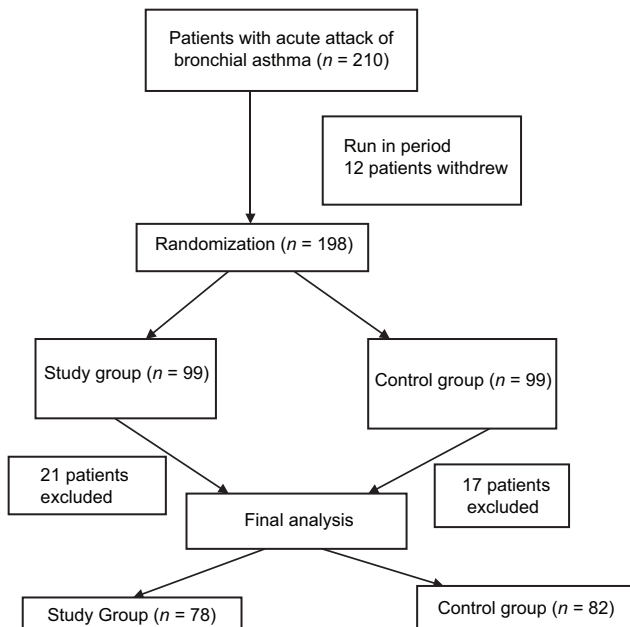
Figure 1: Randomization table

Baseline characteristics of the patients in the two groups were identical [Table 1]. Dyspnea and cough 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 comorbid conditions present in the patients with bronchial asthma. 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. It was also observed that nearly 45% had at least one admission in the previous 1 year, with many patients had more than one admission in the previous year.

The patients in the study group received montelukast 10 mg daily for 15 days till the acute episode subsided. It was observed that improvement in FEV_1 at discharge and at 2 weeks was almost similar in both groups, while at 4 weeks of therapy there was statistically significant improvement in FEV_1 in the study group as compared to the control group ($P < 0.0033$) [Table 2]. However, it is observed that there was no improvement in FVC among the study and control group at any given point of treatment till 4 weeks of therapy [Table 3]. As far as PEFR is concerned, it was observed that there was significant improvement in PEFR at 2 weeks and 4 weeks in the study group as compared to the control group (3.3 ± 1.5 L/s and 3.8 ± 1.8 L/s vs. 2.9 ± 1.2 L/s and 2.9 ± 1.4 L/s respectively) ($P < 0.0376$ and $P < 0.0003$ respectively) [Table 4].

Table 1: Baseline characteristics of the patients

	Study group, *n* (%)	Control group, *n* (%)	*P*
Age group (years)			
18-29	20 (25.6)	18 (22.0)	0.20
30-39	16 (20.5)	16 (19.5)	0.51
40-49	21 (26.7)	24 (29.2)	0.32
50-59	12 (15.4)	13 (15.8)	0.32
>60	10 (12.8)	10 (12.2)	0.30
Mean age (years)	39.9±15.8	42.8±12.8	0.20
Male: female ratio	1:1	1:1	0.79
Duration of illness (years)	7.0±8.5	5.6±4.2	0.29
Mean BMI (kg/m²)	24.0±3.8	23.4±4.3	0.34
Comorbidities	23 (29.5)	28 (34.1)	0.32
Mild exacerbation	40 (51.3)	48 (58.5)	0.34
Moderate exacerbation	38 (48.7)	34 (41.5)	0.34
Previous history of admissions in last 1 year	37 (47.4)	35 (42.7)	0.45

BMI: Body mass index

Table 2: Comparison of forced expiratory volume in 1 s among study and control groups at different intervals of treatment

Time points	Mean±SD		*t*	*P*
	Study group	Control group		
On admission	1.1±0.6	1.2±0.7	−0.6206	0.5358
On discharge	1.4±0.7	1.5±0.7	−0.7263	0.4687
2 weeks	1.7±0.7	1.6±0.7	1.1976	0.2329
1 month	1.9±0.8	1.5±0.6	2.9829	0.0033

SD: Standard deviation

In the present study, it is observed that there was significant mean improvement in FEV_1 values in the study group from the baseline to 1 month, from 1 week to 1 month, and from 2 weeks to 1 month as compared to the control group ($P < 0.0001$, $P < 0.00001$, and $P < 0.0015$ respectively) [Table 5]. Similarly, there was a significant improvement in mean FVC values in the study group from 1 week to 1 month and from 2 weeks to 1 month as compared to the control group ($P < 0.0026$ and $P < 0.0141$ respectively). It was also observed that there was statistically significant improvement in PEFR mean values in the study group from the baseline to 1 month, from 1 week to 1 month, and from 2 to 4 weeks ($P < 0.0074$, $P < 0.00001$, and $P < 0.0016$ respectively).

Table 6 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

Acute exacerbations in bronchial asthma are a frequent event and have got a varied degree of severity, and the response to the treatment varies from individual to individual. The present study was done to assess the efficacy of LTRA, oral montelukast as an add on therapy to the standard therapy for acute attack of bronchial asthma. In the present study, it was observed that almost half of the patients had the moderate severity of bronchial asthma while the remaining half had mild severity of acute attacks. Nearly, one-third of the patients with bronchial asthma were having repeated exacerbations, which may be due to poor control of asthma in these patients.

A total of 160 patients were finally assessed - 78 in the study group and 82 in the control group. In the present study, it was observed that FEV_1 at 1 week and 2 weeks was almost similar in both groups, while at 4 weeks of oral montelukast therapy, there was statistically significant improvement seen. There was a significant mean improvement in FEV_1 values in the study group from the baseline to 4 weeks, from 1 week to 4 weeks, and from 2 to 4 weeks as compared to the control group, which was statistically significant. The mean improvement in FEV_1 was observed to be 21% in the montelukast group as compared to the placebo at the end of 4 weeks. Camargo *et al*.[8] observed a 14.8% improvement in FEV_1 at 2 h from baseline after intravenous montelukast compared with 3.6% for placebo ($P = 0.007$) in patients with acute asthma. Silverman *et al*.[9] has observed a very small increase in FEV_1 after administration of Zafirlukast ($P = 0.04$) at 3.5 h. Similarly, Ramsay *et al*.[5] have observed that oral montelukast produced 15.7% improvement in FEV_1 compared with 7.0% with placebo and 20.7% for the intravenous form. Gaddy *et al*.[10] showed that intravenous

Table 3: Comparison of forced vital capacity among study and control groups at different intervals of treatment

Time points	Mean±SD		*t*	*P*
	Study group	Control group		
On admission	1.5±0.8	1.6±0.8	−0.6266	0.5318
On discharge	1.7±0.7	1.8±0.7	−1.4014	0.1631
2 weeks	2.0±0.7	2.0±0.7	−0.3979	0.6912
1 month	2.1±0.8	2.0±0.7	1.3378	0.1829

SD: Standard deviation

Table 4: Comparison of peak expiratory flow rate among study and control groups at different intervals of treatment

Time points	Mean±SD		*t*	*P*
	Study group	Control group		
On admission	2.2±1.3	1.9±1.2	1.5541	0.1222
On discharge	2.9±1.5	3.0±1.5	−0.1425	0.8868
2 weeks	3.3±1.5	2.9±1.2	2.0973	0.0376
1 month	3.8±1.8	2.9±1.4	3.6865	0.0003

Table 5: Mean difference in forced expiratory volume in 1 s, forced vital capacity and peak expiratory flow rate values among study and control groups at differing intervals

Time points	Mean±SD		*t*	*P*
	Study group	Control group		
Difference from admission to 1 month				
FEV_1 improvement	0.74±0.68	0.35±0.55	4.0317	0.0001
FVC improvement	0.67±0.63	0.44±0.90	1.8623	0.0644
PEFR improvement	1.58±1.54	0.97±1.27	2.7147	0.0074
Difference from 1 week to 1 month				
FEV_1 improvement	0.48±0.64	0.07±0.39	4.8845	0.00001
FVC improvement	0.48±0.62	0.17±0.65	3.0555	0.0026
PEFR improvement	0.85±1.40	−0.10±1.21	4.5931	0.00001
Difference from 2 weeks to 1 month				
FEV_1 improvement	0.17±0.41	−0.03±0.36	3.2328	0.0015
FVC improvement	0.18±0.44	−0.02±0.55	2.4832	0.0141
PEFR improvement	0.47±0.95	0.02±0.84	3.2054	0.0016

FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, PEFR: Peak expiratory flow rate, SD: Standard deviation

Table 6: Number of adverse effects in the study group during 1 month

Adverse effects	Study group, *n* (%)	Control group, *n* (%)	*P*
Headache	5 (6.4)	4 (4.9)	0.35
Muscle pain	3 (3.8)	2 (2.4)	
Rashes	1 (1.3)	1 (1.2)	
Total	9 (11.5)	7 (8.5)	

LTRAs 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*.,[11] 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*.[12]

did not observe any improvement in FEV_1 among children aged 6–14 years 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.*,[10] Silverman *et al.*,[9] and Camargo *et al.*[8]

In the present study, it was observed that there was no improvement in FVC among the study group patients taking oral montelukast and the control group till 4 weeks of therapy. Similar findings have been observed by Silverman *et al.*[9] and Nelson *et al.*[12] 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 that there was significant improvement in PEFR at 2 weeks and 4 weeks in the study group taking oral montelukast as compared to the control group (3.3 ± 1.5 L/s and 3.8 ± 1.8 L/s; and 2.9 ± 1.2 L/s and 2.9 ± 1.4 L/s, $P < 0.0376$, and $P < 0.0003$ respectively). The mean improvement was 12% at 2 weeks and 23% at 4 weeks in the montelukast group as compared to the placebo group. There was also improvement in PEFR mean values in the study group from baseline to 1 month, from 1 week to 4 weeks, and from 2 to 4 weeks as compared to the control group, which was statistically significant. Ramsay *et al.*,[5] 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 with a difference of 57.4 L/min ($P < 0.04$). It was also observed that by the time of discharge, at the end of 4 weeks, the PEFR difference between the two groups had reduced and was nonsignificant and was almost the same in both groups. In another study, Zubairi *et al.*[11] had observed that there was no significant difference in PEFR during the hospital stay and at discharge with oral montelukast therapy. Ferreira *et al.*[13] observed that montelukast group had a 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. The improvement in PEFR in the present study was higher as compared to the other studies. This may be due to the fact that half of the patients had mild exacerbations and they could perform the PEFR maneuver correctly. In this study, diurnal PEFR variability could not be assessed as the 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 handheld Mini-Wright peak flow meters.

In the present study, 11.5% in the study group and 8.5% in the control group developed adverse events which were mild and transient in nature and included headache, muscle cramps, and skin rashes ($P < 0.35$). These side effects due to montelukast are similar to that reported in the literature. Headache (18.4%), flu (4.2%), abdominal pain (2.9%), cough (2.9%), and heartburn (2.1%) have been common side effects reported with montelukast in adults.[14]

Our study observed that during the follow-up of 1 month period, there were 12 exacerbations (15.4%) in the study group while there were 28 exacerbations (34.1%) in the control group. This was not statistically significant ($P < 0.18$). Emerman *et al.*[15] have reported relapse rate of 17% after treatment of acute attack of bronchial asthma over 2-week period, while Rowe *et al.*[16] reported a relapse rate of 14.5% after discharge from acute attack of bronchial asthma. Thus, the relapse rate in the present study is comparable to those reported in other studies. Benjaponpitak *et al.*[17] observed a relapse rate of 29.7% at 8 weeks after discharge and identified the age at onset of asthma before the age of 6 years as an important risk factor. This may help to decrease the relapse rate by more intensive and comprehensive management among patients at high risk.

The study has some limitations. First, the sample size is relatively small. Second, the patients with severe exacerbations were excluded. Both these factors may have impacted on the strength of the difference observed in the two groups. Third, 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 reduced in the patients but did not translate into clinical effectiveness. Finally, this was a single center and a single-blinded study. Hence, the results cannot be generalized to the whole population.

CONCLUSION

In acute asthma exacerbations, the present study showed that additional administration of oral montelukast resulted in significantly higher FEV_1 at 4 weeks and PEFR at 2 weeks and 4 weeks as compared to the standard treatment alone. These findings should be confirmed by conducting a larger population-based clinical study.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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