Original Article

Comparison of oral montelukast with oral zileuton in acute asthma: A randomized, double-blind, placebo-controlled study

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ABSTRACT

Background: Leukotriene modifiers have an established role in the management of chronic asthma but their role in acute asthma is still under evaluation. **Objective:** To study and compare the effects of oral montelukast with oral zileuton in acute asthma. **Materials and Methods:** This study included 120 asthmatics and was conducted from September 2012 to March 2014. Patients were randomized into three different groups to receive montelukast or zileuton or placebo in addition to standard treatment for asthma exacerbation. Peak expiratory flow rate (PEFR) values, details of rescue medication and vital signs were recorded at 6 h, 12 h, 24 h, and 48 h of drug or placebo administration and at discharge. Additional recording was done in the morning (8–10 am) following admission. The primary endpoint was the mean PEFR of each group at these time points; the secondary end point being the need for rescue medications. **Results:** The mean PEFR recordings of the three study groups – placebo, montelukast, and zileuton – respectively, at various time points were as follows: at 6 h (223.25 ± 90.40, 199.00 ± 82.52, 233.75 ± 84.05; $P = 0.240$); at 12 h (271.00 ± 109.38, 251.50 ± 101.44, 309.50 ± 129.63; $P = 0.048$); at 24 h (288.25 ± 114.26, 269.00 ± 107.51, 324.50 ± 127.88; $P = 0.080$); and at 48 h (295.00 ± 114.80, 293.50 ± 113.24, 344.75 ± 119.91; $P = 0.015$); discharge (305.00 ± 118.56, 305.25 ± 119.51, 361.25 ± 119.70; $P = 0.010$). The mean PEFR for the three study groups at 8–10 am on the morning following admission was 268.75 ± 111.43, 252.50 ± 99.99, 306.75 ± 114.44; P = 0.047. Total rescue doses needed were 10, 1, and 0, respectively ($P = 0.049$). **Conclusion:** Zileuton is better than montelukast as an additional drug in acute asthma and results in significant improvement in lung function, and reduction in the need for rescue medications.

KEY WORDS: Acute asthma, montelukast, zileuton

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INTRODUCTION

Acute asthma is a clinical condition commonly managed by emergency health care providers. The treatment options for acute asthma broadly include bronchodilators and corticosteroids.[1] Though corticosteroids are the most potent anti-inflammatory agents, yet they do not suppress inflammatory mediators like leukotrienes – which have an important role in the pathogenesis of asthma.[2] Moreover, pharmacokinetic studies have shown the effects of systemic corticosteroids to be apparent only after 4–6 h of administration.[1] As a consequence of these deficiencies, a need for additional therapeutic options exists and, hence, various drugs have been studied for their efficacy in acute asthma.[3-6] However, the results of these studies have not been very encouraging, which has prompted investigators to probe the utility of leukotriene modifiers, such as montelukast (oral or intravenous) in acute asthma – the usefulness of which in chronic asthma

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is well-established.[7] In this context, the present study was carried out to compare oral montelukast with oral zileuton in acute asthma in patients who were already receiving standard treatment for acute asthma.[8] The study assessed and compared the effects of these drugs on lung function (PEFR) and the need for rescue medications.

MATERIALS AND METHODS

This was a randomized, prospective, placebo-controlled, double-blinded, single-center, comparative study conducted in the department of pulmonary medicine at a tertiary care hospital in South India. The study was initiated after obtaining permission from the institutional ethics committee. Patients presenting to outpatient unit or emergency triage, from September 2012 to March 2014, with a primary diagnosis of acute exacerbation of asthma requiring hospitalization, were included in the study. The inclusion criteria were age between 18 and 65 years, previously diagnosed case of bronchial asthma, a primary diagnosis of acute exacerbation of asthma on presentation, peak expiratory flow rate (PEFR) ≤75% of personal best within the last 12 months or of predicted value, and no other acute pathology complicating the present condition such as cardiac, metabolic, or other respiratory causes. Patients with a history of smoking more than 10 pack years, pregnant females, breastfeeding females, patients on regular leukotriene receptor antagonists or 5-lipoxygenase inhibitors within 2 weeks of presentation, intake of oral or parenteral steroids for >5 days within 1-month of presentation, intake of theophylline within 1-week of presentation, need of intubation before presentation, patients on regular rifampicin, phenytoin or phenobarbitone, and known allergic reaction to montelukast or zileuton were excluded from the study. Informed written consent was taken from the patients in the language understandable to them prior to inclusion.

History, findings of physical examination and laboratory investigations were noted and entered as per a predesigned proforma. The proforma was designed by the authors based on the study requirements, i.e., the data to be captured, taking into consideration earlier studies.[9] However, the proforma was not validated.

Anticipating a minimum difference of 40 l/min in PEFR with a standard deviation of 100 l/min for 80% power at 95% confidence level, 40 subjects were recruited, in each study arm. Enrolled patients had a baseline measurement of PEFR using a mini Wright's PEF meter. After 5 min of baseline PEFR, the patients were randomized into three groups using block randomization (Chit method): A total of 20 envelopes were created. In addition, 42 chits were prepared, with each bearing the letters P, M, and Z (corresponding to placebo, montelukast, and zileuton, respectively) arranged in one of six possible sequences. The possible sequences with the letters PMZ are PMZ,

PZM, MPZ, MZP, ZMP, and ZPM. Seven such sets were prepared (adding up to a total of 42 chits). Two chits were placed in each of the twenty envelopes, and the remaining 2 chits were discarded. While allocating cases to a group, envelopes were opened one by one, chits were picked up and cases allocated to each group as per the letter sequence.

Patients in all the three groups received standard treatment for asthma exacerbation, i.e., nebulized salbutamol 2.5 mg 6th hourly, nebulized ipratropium bromide 500 mcg 6th hourly and intravenous methyl prednisolone 40 mg 8th hourly. Rescue medications comprised nebulized salbutamol 2.5 mg, given on need basis. Additional oxygen and methylxanthines were given, if indicated. Patients and the investigators were kept blinded regarding the study medication, and a third observer distributed and administered the tablets from the packs – montelukast, zileuton, and placebo – to the patients as per the randomization code. The third observer had no other role in the study. Patients randomized to Group 1 received oral montelukast 10 mg tablet with a placebo at enrollment and two placebo tablets after 12 h. Patients randomized to Group 2 received two oral zileuton CR 600 mg tablets twice a day. Patients randomized to group 3 received two placebo tablets twice daily. The investigational medications were continued till the patient was discharged from the hospital or developed any adverse effects to these drugs.

PEFR values, details of rescue medication, and vital signs (pulse rate, blood pressure, respiratory rate, and SpO_2 by pulse oximetry) were recorded at 6 h, 12 h, 24 h, and 48 h of drug or placebo administration and at discharge. Additional recording of these parameters was done in the morning (8–10 am) following admission.

The primary endpoint was the mean PEFR of each group at different measured time points following treatment. Secondary end point was the need for rescue medications in each group.

Statistical analysis

Repeated measures ANOVA with baseline PEFR set as a covariate was used to analyze mean PEFR of each group at different measured time points after initiation of treatment. Univariate ANOVA with baseline PEFR as a covariate was used to analyze mean PEFR at 8–10 am on the morning following admission. Fisher's exact test and Chi-square test were used to analyze the need for rescue medications and the requirement of methylxanthines and oxygen in the various groups. Time to discharge data was analyzed using Kruskal–Wallis nonparametric analysis and expressed as median and interquartile ranges. Analysis was performed using SPSS 15.0 (SPSS, South Asia, Bangalore) and the means and percentages were expressed in tables and graphs.

RESULTS

A total of 153 patients were screened for eligibility of inclusion into the study, of which 120 patients met the inclusion criteria. Of the enrolled patients, 40 patients were randomized to enter the placebo arm, 40 patients to the montelukast arm and 40 patients to the zileuton arm. All 120 patients who were enrolled completed the study and results were analyzed at the end of the study.

Baseline characteristics of patients are mentioned in Table 1. The montelukast group had more patients with severe exacerbation and lesser with mild-moderate exacerbation, but there was no significant difference between the groups so far as the severity of exacerbations was concerned ($P = 0.07$). None of the patients had life-threatening asthma at presentation. Seventy-two patients (60%) received antibiotics.

Primary outcome measures
The mean PEFR for the three study groups at baseline and over the hospital stay was analyzed using repeated measures ANOVA with *post hoc* analysis, with baseline PEFR set as the covariate. On comparing with placebo, zileuton group had significantly higher mean PEFR values ($P = 0.007$) whereas montelukast group did not differ significantly ($P = 0.181$) [Figure 1]. The results of univariate ANOVA analysis of data are shown in Table 2. The mean PEFR for the three study groups at 8–10 am on the morning following admission was analyzed using univariate ANOVA, with baseline PEFR set as the covariate. Again on comparing with placebo, zileuton group had significantly higher mean PEFR values ($P = 0.041$) whereas montelukast group did not

differ significantly ($P = 0.651$). The results are shown in Table 3.

Secondary outcome measures
The secondary end points were analyzed using Chi-square test. Five patients in the placebo group required rescue medications, one of them requiring thrice, three patients requiring it twice, and one patient requiring it once. One patient in the montelukast group required rescue medication once. However, no patients in the zileuton arm needed rescue medications [Table 4]. This difference in the requirement for rescue medications in the montelukast and zileuton groups compared to the placebo group met statistical significance ($P = 0.049$).

Need for methylxanthines and oxygen
The need for methylxanthines and oxygen in three groups is shown in Table 5. The difference in the requirement

Figure 1: Mean peak expiratory flow rate at different time points after initiation of treatment (with baseline peak expiratory flow rate [167.92 l/min] set as the covariate)

Table 1: Baseline patient characteristics (*n*=120)

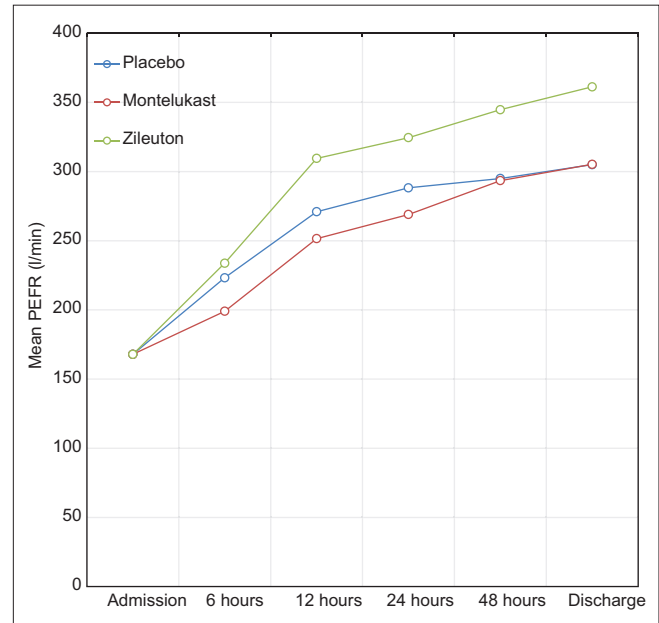| Patient characteristic	Placebo	Montelukast	Zileuton
Total number of patients (*n*)	40	40	40
Age in years: Mean (SD)	52.1 (14.0)	49.4 (8.9)	49.6 (15.8)
Male:female	17:23	14:26	18:22
BMI (kg/m²): Mean (SD)	23.1 (4.6)	22.9 (3.5)	22.4 (4.3)
Severity of exacerbation *n* (%)			
Mild or moderate	10 (25)	5 (12.5)	9 (22.5)
Severe	30 (75)	35 (87.5)	31 (77.5)
Asthma history in years: Mean (SD)	8.3 (7.0)	10.8 (7.8)	9.9 (9.1)
Patients with concomitant allergic rhino-sinusitis: *n* (%)	22 (55)	23 (57.5)	26 (65)
Never smokers; *n* (%)	37 (92.5)	38 (95)	38 (95)
Comorbidities: *n* (%)			
Hypertension	14 (35)	10 (25)	7 (17.5)
Diabetes mellitus	9 (22.5)	7 (17.5)	6 (15)
Coronary artery disease	4 (10)	5 (12.5)	0 (0)
Treatment received prior to enrollment: *n* (%)			
Inhaled corticosteroids plus bronchodilators	27 (67.5)	18 (45)	25 (62.5)
Only inhaled bronchodilators	3 (7.5)	6 (15)	3 (7.5)
Not on any treatment	10 (25)	16 (40)	12 (30)

SD: Standard deviation, BMI: Body mass index

Table 2: Mean peak expiratory flow rate at different time points after initiation of treatment (*n*=120)

Time after treatment	Mean PEFR±SD (l/min) (*n*=40)			*P*
	Placebo	Montelukast	Zileuton	
Baseline	181.5±82.9	147±68.2	175.3±58.3	0.070
6 h	223.25±90.40	199.00±82.52	233.75±84.05	0.240
12 h	271.00±109.38	251.50±101.44	309.50±129.63	0.048
24 h	288.25±114.26	269.00±107.51	324.50±127.88	0.080
48 h	295.00±114.80	293.50±113.24	344.75±119.91	0.015
Discharge	305.00±118.56	305.25±119.51	361.25±119.70	0.010

The *P* values mentioned giving information regarding the presence or absence of any significant difference among the three groups at various time points (using univariate ANOVA). PEFR: Peak expiratory flow rate, SD: Standard deviation

for methylxanthines and oxygen in the montelukast and zileuton groups compared to the placebo group was not statistically significant ($P = 0.237$).

Hospital days and condition at discharge

The patients were discharged based on clinical improvement, improvement in vital signs and improvement in PEFR though there were no strict prescribed criteria for discharge. All patients, except one, showed a significant improvement in vital signs and PEFR at the time of discharge. One patient from placebo group who did not exhibit clinically significant change from baseline values of vital signs and PEFR was discharged based on significant symptomatic improvement. There was a significant difference in the time to discharge between the various groups ($P = 0.022$). The number of hospital days expressed as median (interquartile ranges) for placebo, montelukast, and zileuton groups were 5 (4–6.5), 6 (5–9), and 5 (4–6), respectively.

None of the study participants required intubation. There were no deaths during the study. No adverse event was reported during the study.

DISCUSSION

Leukotriene receptor antagonists like montelukast have a well-defined role in the management of chronic asthma; and they have been subjected to a number of studies for evaluating their role in acute asthma. There has been some evidence in support of usefulness of montelukast in acute asthma. In a study done in the USA, Camargo *et al.* demonstrated a rapid and significant improvement in FEV_1, noted at 10 min and over 2 h after administration of intravenous montelukast, when compared with placebo. Later, these results were reproduced in a study with a larger sample size ($n = 583$).[10,11] A recent Japanese study by Adachi *et al.* also found that intravenous montelukast was significantly more effective than placebo in the improvement of FEV_1 in the acute asthma setting.[12] On comparing the effect of intravenous versus oral montelukast in a randomized placebo-controlled study in patients with acute asthma faster onset of action and better improvement in FEV_1 was reported with intravenous montelukast. However, oral montelukast group also demonstrated significant improvement in FEV_1 when compared to placebo.[13] Investigators from the United Kingdom, in a randomized, placebo-controlled, single-center study, involving a total of 73 patients with acute asthma randomized to receive oral montelukast or placebo in addition to standard treatment, reported significantly higher PEF values recorded on the morning following admission ($P = 0.046$) in the montelukast arm.[9]

In contrast, the results of our study showed that oral montelukast, when used in addition to standard treatment,

Table 3: Mean peak expiratory flow rate on the morning following admission (8-10 am) (*n*=120)

Time after treatment	Mean PEFR±SD (l/min) (*n*=40)			
	Placebo	Montelukast	Zileuton	*P*
8-10 am on the morning following admission	268.75±111.43	252.50±99.99	306.75±114.44	0.047

PEFR: Peak expiratory flow rate, SD: Standard deviation

Table 4: Need for rescue medications in each group (*n*=120)

Number of times rescue medications were used	Placebo	Montelukast	Zileuton
	n=40 (100%)	*n*=40 (100%)	*n*=40 (100%)
None	35 (87.5)	39 (97.5)	40 (100)
Once	1 (2.5)	1 (2.5)	0
Twice	3 (7.5)	0	0
Thrice	1 (2.5)	0	0
Total usage of rescue medications	10	1	0

Baseline mean PEFR±SD (l/min) for placebo, montelukast and zileuton were 181.5±82.9, 147±68.2, and 175.3±58.3, respectively. PEFR: Peak expiratory flow rate, SD: Standard deviation

Table 5: Need for additional methylxanthines and supplemental oxygen in each group (*n*=120)

Additional medications	Patients requiring additional medications *n* (%)		
	Placebo	Montelukast	Zileuton
	n=40 (100%)	*n*=40 (100%)	*n*=40 (100%)
Methylxanthines	17 (42.5)	15 (37.5)	9 (22.5)
Oxygen	1 (2.5)	2 (5)	1 (2.5)

did not produce statistically significant improvement in PEFR ($P = 0.181$) compared to placebo. However, the requirement for rescue medications in the montelukast group was significantly less compared to the placebo group ($P = 0.049$). There are other studies which have also questioned the role of montelukast in acute asthma. A study from Portugal reported no significant differences between montelukast and placebo groups in terms of improvement in PEFR and duration of stay in the emergency room in a study involving 20 adults with acute asthma but showed trends in favor of montelukast in terms of lesser requirement for systemic therapy with aminophylline or steroids ($P = 0.03$).[14] The results of this study are identical to ours so far as lack of improvement in PEFR is concerned. However, in our study, the need for additional requirement of methylxanthines, even though lesser among montelukast group, failed to show any statistical significance ($P = 0.956$). A study done in the tertiary care hospital in Turkey randomized 70 patients with acute asthma to receive placebo alone, prednisolone alone or montelukast together with prednisolone; in addition, each group receiving nebulized beta-2 agonists. Though the patients receiving both prednisolone and montelukast had significantly higher percentage change in PEF from baseline over a 24 h period in comparison with placebo group ($P < 0.05$), the percentage change in PEFR in comparison with patients receiving prednisolone

alone did not show any statistical significance ($P = 0.064$). Moreover, patients receiving both prednisolone and montelukast neither had significantly better Borg dyspnea scores ($P = 0.34$) nor lesser need for rescue medications (0.064) compared to prednisolone group.[15] The results of this study were similar to our study in terms of the primary endpoint (PEFR trend), but the results of secondary endpoints – need for rescue medications – were contrasting. Results obtained in a recent randomized, placebo-controlled study by Zubairi *et al.*, in which 100 patients were randomized to receive either montelukast or placebo, in addition to standard treatment with systemic steroids and nebulized bronchodilators, have raised further doubts There was no statistically significant difference between the treatment groups during hospital stay ($P = 0.20$ at day 2 and $P = 0.47$ at day 3) and at the time of discharge ($P = 0.15$), in terms of both FEV_1 and PEF. The difference between the time to discharge in both groups was also not statistically significant ($P = 0.90$).[16] In our study, the time to discharge in the montelukast group was greater than in placebo group. As is apparent from the contrasting results of the studies on montelukast, oral montelukast is not currently recommended for use in acute asthma; however, to ascertain the role of intravenous montelukast in acute asthma, more research is required.[8]

However, in spite of these contrasting results, there may still be a case for the use of leukotriene modifiers in this setting, and this perhaps was underscored by the results of the zileuton arm of our study. Acute bronchodilator effect has been observed with use of zileuton, but most of the earlier studies on zileuton have been carried out in patients with chronic stable asthma and not during episodes of acute asthma.[17-20] In addition, studies comparing the efficacy of zileuton and montelukast are also few. In one such study, involving mild to moderate chronic stable asthmatics, the investigators reported significant improvement in PEFR, reduction in the mean overall symptom intensity score, and also reduced but not significantly different adverse event rate in zileuton group when compared to the montelukast group.[21] Our study tried to address both the issues of zileuton use in acute setting and its comparison with montelukast. Our results show that zileuton, when used in such a setting, produced statistically significant improvement in PEFR ($P = 0.007$) compared to the placebo group, unlike montelukast which failed to demonstrate such an effect. The higher PEFR values were maintained throughout the hospital stay– persisting till the discharge. Moreover, the need for rescue medications in the zileuton group was also significantly less compared to the placebo group. With respect to this outcome measure, the results were similar in montelukast group as well. The need for methylxanthines and oxygen were also comparatively lesser among zileuton group, though it failed to reach statistical significance ($P = 0.055$). Though the time to discharge in the zileuton group was shorter in comparison with the placebo group, it was not statistically significant ($P = 0.187$). There were no adverse effects in the zileuton arm during the study.

However, more frequent dosing remains a drawback with zileuton. These results will continue to stoke interest in the use of leukotriene modifiers in acute asthma, and perhaps the last word on this issue has not been said yet.

The limitation of our study was the use of PEFR as an indicator of airflow obstruction as many studies done in this context have used FEV_1 - a better indicator. We also did not assess biological markers like urinary cysteinyl leukotriene levels or subjective measures of clinical improvement like Borg Dyspnea Score. The addition of these measures could have strengthened the results. There were no set criteria for discharging patients, and this could have affected the results regarding the length of hospital stay. As our study was a single center study on a localized population in South India, a larger multicenter study is required to generalize these results to a larger population.

CONCLUSION

Addition of oral zileuton to standard treatment of acute asthma results in significant improvement in lung function and reduction in the need for rescue medications when compared to standard treatment alone. However, addition of montelukast to standard treatment does not improve lung functions significantly but reduces the need for rescue medications. Zileuton is better than montelukast as an additional drug in acute asthma.

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Conflicts of interest
There are no conflicts of interest.

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