The Effects of Oral Montelukast on Spirometric Results & Hospital Length of Stay in Patients With Acute Exacerbation of COPD

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Abstract

Background: Leukotriene receptor antagonists have been studied in the management of moderate to severe stable COPD with controversial results. However, there is very little information on their use in acute exacerbations of COPD.

The aim of this study is to find whether Leukotriene receptor antagonists may accelerate the lung function recovery & shorten the period of hospital stay when given in acute exacerbation of COPD.

Patients & Methods: 54 patients were included in this study; their mean age was 59 years (SD +/− 7.50). The majority were males (72%).

The trial was conducted at the Merjan teaching Hospital to assess the efficacy of oral montelukast on patients who were admitted to the hospital with acute exacerbation of COPD. The study group was randomly divided into group I (30 patients) which were given montelukast along with standard therapy throughout the hospital stay & group II (24 patients) which were given standard therapy alone. Improvements in lung function and duration of hospital stay were monitored.

Results: There was better improvement in pulmonary function test results at discharge & on follow up 7 days post discharge & less duration of hospital stay in group I patients compared to group II. No serious adverse effects were noted during the course of the study.

Conclusion: Our study suggests that there is a benefit of addition of oral montelukast over conventional treatment in the management of acute exacerbation of COPD.

Keywords: montelukast . spirometry . Hospital length of stay . Acute exacerbation . Chronic obstructive pulmonary disease

الخلاصة

اجريت الدراسة الحالية على 54 مريض مصاب بتهيج حاد لالتهاب القصبات المزمن ادخلوا الى الردهة العامة في مستشفى مرجان للفترة من اذار 2012 ولغاية اذار 2014 لمعرفة تاثير اضافة عقار المونتيلوكاست للعلاج النموذجي المستخدم لعلاج هذه الحلات على نتائج وظائف الرئة للمرضى وعلى فترة رقودهم في المستشفى. حيث تم تقسيم المرضى الى مجموعتين, المجموعة الاولى (30 مريض) تم اعطائهم عقار المونتيلوكاست اضافة للعلاج النموذجي والمجموعة الثانية (24 مريض) تم اعطائهم العلاج النموذجي فقط. تم قياس وظائف الرئة للمرضى عند دخولهم للمستشفى وعند الخروج و عند مراجعتهم سبعة ايام بعد الخروج. ومن نتائج الدراسة الحالية لوحظ تحسن في وظائف الرئة لمرضى المجموعة الاولى وفترة بقاء اقل في المستشفى مقارنة بمرضى المجموعة الثانية مما يدل على وجود فائدة لاضافة علاج المونتيلوكاست للعلاج النموذجي

كلمات مفتاحية : مونتيلوكاست, السبايروميتر , التهاب القصبات المزمن , نوبات تهيجية

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease; its pulmonary component is characterized by airflow limitation that is not fully reversible, usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (GOLD, *Executive summary* 2006).

Acute exacerbation of COPD is defined as an acute increase in dyspnea, sputum volume, and/or sputum purulence without other attributable cause

COPD exacerbations were responsible for 726,000 hospitalizations and 119,000 deaths in the United States (Mannino *et al*., 2002).

The usual management of acute exacerbations of COPD has not changed in the last 30 years & consists of bronchodilators, corticosteroids, and antibiotics; the only exception is the use of noninvasive ventilation.

Leukotrienes are inflammatory mediators that are derived from arachidonic acid, initially through 5-lipoxygenase enzymatic activity. Subsequent enzymatic steps generate either LTB4, which mediates neutrophil and T-cell chemotaxis, or the cysteinyl leukotrienes (LTC4, LTD4, LTE4), which cause smooth muscle contraction, tissue edema, inflammatory cell chemotaxis, and mucus production (Peters-Golden, 2008).

The reasons for our study of montelukast in Acute exacerbation of COPD was because many studies show the role of both of the above classes of leukotrienes in the pathophysiology of Acute exacerbation of COPD (Crooks *et al.,* 2000; Biernacki *et al.,* 2003; Shindo *et al.,* 1997; Hill *et al.,* 1999; Nannini *et al.,* 2003), and another 2 clinical studies, which have found increased serum and exhaled breath leukotrienes levels in patients with COPD despite corticosteroid use (Seggev *et al.,* 1991; Montuschi *et al.,* 2003) (indicating that any benefit of leukotrienes blockade might be additive to those of corticosteroids).

Clinical trials of anti-leukotriene therapy in COPD (Despite the above data) have focused only on patients with chronic stable disease (Gompertz *et al.,* 2002; Celik *et al.,* 2005). To date, there are only few published randomized trials of anti-leukotriene therapy in acute exacerbation of COPD. However, a prior randomized controlled trial demonstrated rapid improvements in FEV1 and a reduction in treatment failure with the use of leukotriene receptor blockade for the treatment of asthma exacerbations in the emergency department (Camargo *et al.,* 2003).

Based on studies of mediators of inflammation in COPD, clinical trials of anti-leukotriene therapy in stable COPD, and a clinical trial of anti-leukotriene therapy in exacerbations of asthma, we hypothesized that anti-leukotriene therapy would provide a novel therapeutic approach to Acute exacerbation of COPD requiring hospitalization. Our primary goal was to reduce hospital length of stay.

Montelukast is the most commonly used cysteinyl leukotrienes receptor 1 (CysLT-1) antagonist. It has been shown to improve symptoms and lung function (FEV1) within 15 minutes of administration in chronic asthma with its effects lasting for a period of at least 24 hours [Dockhorn RJ *et al.,* 2000].

Patients and method

The study was conducted over a period of two years from March 2012 to March 2014. All patients presenting either to the emergency department or outpatient clinics of Merjan teaching hospital requiring hospitalization with acute exacerbation of COPD were screened for inclusion in the study.

Fifty four patients were included in this study; their mean age was 59 years (SD +/− 7.5). The majority were males (72%).

The study group was randomly divided into two groups

*** Group I (30 patients) which were given oral montelukast sodium (10 mg once daily) along with standard therapy throughout the hospital stay

*** Group II (24 patients) which were given standard therapy alone.

The standard therapy included nebulized salbutamol, a 14-day course of systemic corticosteroids beginning with at least 40 mg of prednisone (or its equivalent) per day and a course of an antibiotic selected on the basis of local resistance patterns to S. pneumonia, H. influenza, and M. catarrhalis.

The inclusion criteria included a diagnosis of acute exacerbation COPD (defined as an acute increase in dyspnea, sputum volume, and/or sputum purulence without other attributable cause). Other inclusion criteria were ≥10 pack-years smoking history and an FEV1 <60% predicted at time of inclusion or an inability to perform

spirometry due to dyspnea.The patients with the following conditions were excluded from the study; patients with FEV1 > 70% predicted or PEF > 300 L/min, concomitant therapy with systemic corticosteroids or leukotriene modifiers at any time in the past 4 weeks at the time of admission, any concurrent acute medical condition like myocardial infarction, congestive cardiac failure, diabetic ketoacidosis or shock, acute respiratory failure requiring mechanical ventilation, and improvement in symptoms after being included into the study leading to discharge from the emergency department. Patients who were unwilling to be enrolled in the study were also excluded.

The patients underwent a baseline spirometry testing soon after enrollment.

A brief questionnaire was used to obtain information about the duration, severity and treatment of COPD.

The spirometry was done using MIR spirolab III. The spirometry test was repeated three times. Each test was performed within three minutes of the previous one. The spirometry was done on admission and discharge & on follow up 7 days post discharge.

The primary outcomes of the study were

a) Improvement in lung function measured as FEV1, FVC & FEV1/FVC ratio over the course of hospital stay, discharge & 7 days post discharge.

c) Duration of hospital stay.

Results

The baseline characteristics of both study groups are shown in table 1

Subjects characteristics	Group 1 (30 patients)	Group 2 (24 patients)	p- value
Age	62 ± 6	61± 9	0.24
Men	22	17	0.36
Current smoking	44 %	41 %	0.45
Spo2 (without o2) on admission	87 %	88 %	0.56
Baseline FEV1 (L)	0.79 ± 0.49	0.85 ± 0.30	0.30
FEV1 % predicted	32 ± 11	32 ± 12	0.86
Baseline FEV1/FVC (%)	44 ± 12	40 ± 10	0.41

Data are presented as mean ± SD or percentage, BD denotes bronchodilator.

There were no significant differences in the baseline characteristic between the two study groups.

*** There was a significant difference in the pulmonary function test results between both study groups at discharge from the hospital and 7 days post discharge.

The spirometric results at discharge from the hospital are shown in table 2

Spirometric results	Group 1 (30)	Group 2 (24)	P – value
FEV1 (L)	1.17 ± 0.54	0.93 ± 0.26	0.001
FEV1 (% predicted)	40 ± 9	36 ± 13	0.001
FVC	2.61 ± 0.78	2.23 ± 0.98	0.001
FEV1/FVC	44 ± 7	41 ± 3	0.2

Data are presented as mean ± SD or percentage

***The patients who received montelukast (group 1) had a mean FEV1 of 1.17 ± 0.54 L/min while those on conventional treatment (group 2) had a mean FEV1 of 0.93 ± 0.26 L/min on discharge (p = 0.001). Similar trend was seen in the FVC, where the mean values for group 1 and group 2 patients were 2.61 ± 0.78 L/min and 2.23 ± 0.98 L/min respectively (p = 0.001) (Table 2 & figure 1).
The spirometric results at 7 days from discharge from the hospital are shown in table 3

Spirometric results	Group 1 (30)	Group 2 (24)	P – value
FEV1 (L)	1.29± 0.86	0.97 ± 0.35	0.001
FEV1 (% predicted)	42 ± 1	37 ± 23	0.001
FVC	2.83 ± 0.72	2.42 ± 0.62	0.001
FEV1/FVC	46 ± 12	42 ± 6	0.001

The most remarkable differences in pulmonary function test results were noted at 7 days from discharge from hospital were the mean FEVI group 1 patients was 1.29± 0.86 L/ min whereas in group 2 patients was 0.97 ± 0.35 L/ min (p = 0.001). Similar results were noted in FVC values it was in group 1 patients 2.83 ± 0.72 L/ min & in group 2 patients 2.42 ± 0.62 L/ min (p = 0.001).

The study also shows a significant difference in the length of hospital stay where it was lower in group 1 patients 3.84 ± 2.61 days & higher in group 2 patients 4.84 ± 5.69 days (p = 0.001).

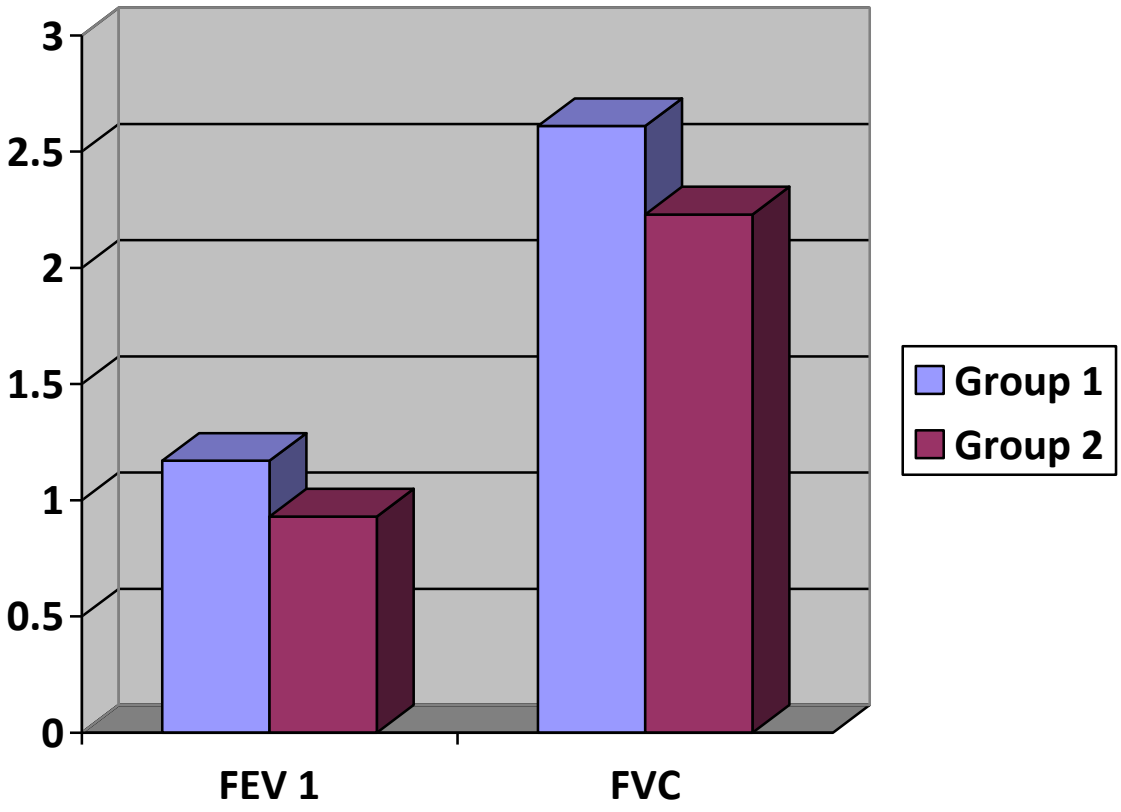

Figure 1 the results of FEV1 & FVC in both study groups are expressed as L/min

Discussion

Many laboratory and clinical studies suggest an important role for leukotrienes in the pathogenesis of inflammation in stable COPD. Expression of two LTB4 receptors, BLT1 and PPARα, is increased in alveolar macrophages and airway wall leukocytes in surgical lung specimens from patients with COPD (Marian E *et al.*, 2006). LTB4 levels are elevated in exhaled breath condensate (10, Kostikas K *et al.*, 2005), sputum (Kostikas K *et al.*, 2005) and serum (Seggev JS *et al.*, 1991) in patients with stable COPD as are plasma levels of the cysteinyl leukotriene, LTC4 (Nannini LJ Jr *et al.*, 2003). To date, 2 clinical trials of anti-leukotriene therapy in stable COPD have been published (Gompertz S *et al.*, 2002 ; Celik P *et al.*, 2005).

The first study is compared daily therapy with montelukast to placebo in 117 patients over 2 months (Celik P *et al.*, 2005). Significant improvements in FVC, FEV1, PaO2 and St. George's Respiratory Questionnaire (SGRQ) scores ($p < 0.05$) were observed in the montelukast group with no comparable improvements in the placebo group.

The second was a trial of the effect of an oral leukotriene synthesis inhibitor BAYx1005 (500 mg twice daily) on sputum biomarkers (Gompertz S *et al.*, 2002). Sputum LTB4 levels were reduced, but no differences were observed in sputum myeloperoxidase concentration or neutrophil chemotaxis between the 2 treatment arms.

Few studies also support a possible role for leukotrienes in acute exacerbation of COPD. Two prior studies showed that blood LTE4 levels were elevated in acute exacerbations and that levels decreased with treatment (Shindo K *et al.*, 1997 ; Pinto-Plata VM *et al.*, 2007). Similarly, sputum and exhaled breath condensate LTB4 levels are elevated in acute exacerbation of COPD and decline with treatment (Biernacki WA *et al.*, 2003; Shindo K *et al.*, 1997 ; Hill AT *et al.*, 1999). In an accompanying in vitro study, Crooks and colleagues (Crooks SW *et al.*, 2000) showed that LTB4 contributed approximately 30% of total neutrophil chemotactic activity in the sputum of these subjects during acute exacerbations.

Our study shows that the use of montelukast, when added to usual treatment of acute exacerbation of COPD, resulted in improvement of clinical features (manifested by improving breathlessness), more rapid improvement in pulmonary function test results & shorter duration of hospital stay compared to the other study group, Supporting the results of the above studies which show clear evidence of effects of the leukotriene inhibitor on leukotriene levels in patients with COPD.

The patients who were included in this study had relatively severe COPD before the start of the study which might have influenced the likelihood that leukotriene antagonism would be beneficial during an exacerbation. Approximately 37 % of our patients were using home oxygen therapy before hospital admission, and 68 % have history of a hospital visit for COPD in the last year. The spirometric data available before the current study (before this admission) suggest that more than half of the subjects had GOLD stage III and IV disease. Therefore, studying patients admitted to the hospital with acute exacerbation of COPD with relatively severe COPD at baseline, could limit the absolute benefit of interventions made during exacerbations through leukotriene antagonism & only results in mild but statistically significant clinical & spirometric benefit.

In summary, the important findings of this study were that we found clinically& statistically significant effect of montelukast on hospital length of stay & pulmonary function test results through leukotriene antagonism which according to the results of the above study reduces cysteinyl leukotriene levels in hospitalized patients with

acute exacerbation of COPD. Whether this pharmacologic effect leads to improvements in all patients with acute exacerbation of COPD is uncertain because of the limited number of patients included in this study. Finally, the use of montelukast in patients with acute exacerbation of COPD has no significant adverse effects noted during the study period.

These safety data, obtained in relatively sick patients with acute exacerbations of lung disease, may encourage the development of further clinical trials of this therapy in stable COPD or in other inflammatory diseases.

Recommendation

The results of this study should encourage the design of another prospective study with larger sample size to assess the effect of montelukast on the clinical outcome in patients with acute exacerbation of COPD because even modest improvement will reduce the high cost and health impact of those acute exacerbations which require hospitalizations.

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