Original Article

Efficacy of montelukast when added with inhaled corticosteroids on mild-to-moderate asthmatic patients

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ABSTRACT

Objective: Asthma is an inflammatory disease characterized by recurrent attacks of breathlessness and wheezing. Inhaled corticosteroids (ICS) play an important role in the management of asthma. Reduction of ICS dose with any other drug combination may therefore be of clinical significance. **Methods:** A total of 118 Patients with mild to moderate asthma were enrolled in this randomized controlled study from the pulmonology/ medicine unit in the tertiary care hospital. **Results:** Patients were randomized into two groups viz., control group(n=59) and the treatment group(n=59).Control group patients received budesonide 800 mg twice a day and the treatment patients received 400 mg budesonide twice a day along with Montelukast 10 mg. Pulmonary function test was assessed at the baseline and on follow up days. No significant difference was observed with respect to socioeconomic and educational status of patients between control and treatment groups. Improvement observed was more in control group value (43%) than in treatment group value (25%).Even though 12% FEV1 improvement were observed, the rate of improvement was not significant ($p>0.5$). There is no serious adverse drug reaction among the tested groups. **Conclusion:** The study concluded that addition of Montelukast 10 mg to the inhaled Budesonide is an effective and alternative treatment option to doubling the dose of inhaled Budesonide..

Keywords: Antileukotrienes, asthma, budesonide, FEV_1, inhaled corticosteroids, montelukast, spirometry

INTRODUCTION

Bronchial asthma is an inflammatory disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person.[1] This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated.[2] In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs.[3] According to the World Health Organization (WHO) statistics, bronchial asthma affects 300 million people. Asthma prevalence increases globally by 50% every decade. The most striking increase in asthma prevalence is seen among children.[4] About 80% of asthma deaths occurred in low- and lower-income countries. In the 2014 year, the most recent revised global estimate of asthma suggests that as many as 334 million people have asthma and that the burden of disability is high. In India, it is estimated at more than 15 million patients.[5] It is reported that 227 disability-adjusted life year per 100,000 peoples. Asthma constitutes 0.2% of all deaths and 0.5% of national burden of diseases.[6]

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MATERIALS AND METHODS

Study site

The study was carried out at major referral hospital. Hospital has 100-bedded general medical department which is well equipped with modern apparatus. Hospital has various departments with well-qualified staff (medicine, surgery, gynecology, psychiatrics, pediatrics, dermatology, oncology, and orthopedics).

Study design

It is an observational prospective study.

Study duration

The study was conducted within a time period of 6 months.

Study subjects

The inclusion and exclusion criteria for study are as follows:

Inclusion criteria

(a) Either of both sexes (male and female)
(b) Age group 18–65 years
(c) Mild-moderate asthmatic patients (FEV_1 60–80% predicted)

Exclusion criteria

(a) Cardiac patients
(b) COPD patients
(c) Pregnant and nursing women

Method of study

The patients for this study were recruited based on inclusion and exclusion criteria. The patients were categorized as mild-moderate asthmatic patient based on their pulmonary function test, as their FEV_1 value between 60 and 85%. The patients were randomly assigned into two treatment groups, control group and treatment. The control group was treated with inhaled budesonide 800 mg twice a day (bid) and the treatment group with inhaled budesonide 400 mg twice a day (bid) plus tablet montelukast 10 mg. All patients could take short-acting β-agonist in case of an asthmatic crisis. The pulmonary function test (PFT), peek expiratory function test (PEFT), chest X-ray, absolute eosinophil count (AEC), and clinical symptoms were examined. The clinical symptoms and diagnostic parameters were evaluated in day 1, 15, 45, and 75 of the treatment.

RESULTS

A total of 118 patients were enrolled in this study and their demographic data, clinical symptoms, and diagnostic parameters were collected. The patients were randomly assigned into two groups. Fifty-nine were assigned into the control group and 59 to the treatment group. After randomization, 13 patients (11%) were withdrawn after randomization due to loss to follow up. The reasons for loss of follow-up were asthma worsening (5% and 8%), non-compliance (3% and 2%), and other reasons (3% and 3%) in the control group and treatment group, respectively.

The patients were categorized into different age groups (18–20 years), (21–30 years), (31–40 years), (41–50 years), and (51–60 years) in both the control and treatment groups, as according to Table 1. The smoking status of patients according to categories smokers, non-smokers, and former smokers, shown in Tables 2 and 3, shows the sex distribution of patients. The symptomatic improvement of patients according to day 1 and day 75 is included in Table 4. Table 5 contained number of asthma attack more than 2 per week in percentage as well as Table 6 contained number of times using asthma rescue drug per week. Table 7 includes asthma triggering factors such as exercise, exposure to cold, smoking, dust, irritants, smoke, and some other factors. Mean and standard deviation in PEFR included in Table 8 as well as mean and standard deviation in FEV_1, as shown in Table 9. At the end, improvement in FEV_1 is shown in Tables 10 and 11.

Table 1: Etiology of asthma[7]

Endogenous factor	Environment factor	Trigger factor
Genetic predisposition	Indoor allergens	Allergens
Atopy	Outdoor allergens	Upper respiratory tract viral infections
Airway hyperresponsiveness	Occupational sensitizers	Exercise and hyperventilation
Gender	Passive smoking	Cold air
	Respiratory infections	Sulfur dioxide, drugs (aspirin, β-blockers)
		Irritants (paints, fumes, sprays)

Table 1a: Age distribution of patients in percentage

Age	Groups				Total patients
	Control		Treatment		
	n	%	*n*	%	
18–20 years	4	8	5	10	9
21–30 years	12	23	16	32	28
31–40 years	14	27	13	25	27
41–50 years	13	25	13	25	26
51–60 years	9	17	4	8	13

Table 2: Classification of asthma based on PFT[8]

Class	Frequency of attack	Nighttime attack	Lung function
Mild intermittent	<2 attacks weekly	<2 times per month	FEV_1 or PERF> 80% predicted, but PERF variability <20%
Mild persistent	>2 attacks per week, but <1 attack daily	> 2 times per month	FEV_1 or PERF> 80% predicted, but PERF variability 20–30%
Moderate persistent	Daily attacks	>1 time per week	FEV_1 or PERF >60%–<80%, PEFR variability >30%
Severe persistent	Continuous attacks	Frequent/daily	FEV_1 or PERF< 60%, >30% PEFR variability

DISCUSSION

Improvements in the asthma exacerbation were measured by the significant lowering percentage of daytime symptoms after the 10-week treatment. The montelukast+ budesonide group had shown reduction in percentage level of asthma daytime symptoms and night symptoms than that of budesonide 800 mg group. Number of asthma attacks was observed after 10-week treatment and was found to be decreasing in higher rate in montelukast-treated group than the budesonide group. Moreover, the improvement in PEFR, 12% improvement in FEV_1, and less need of asthma rescue therapy indicate the improvement in the montelukast treated patients.

Table 3: Sex distribution in percentage

S.no	Sex	Groups	
		Control (%)	Treatment (%)
1.	Male	58	55
2.	Female	42	45

Table 4: Symptomatic improvement in percentage

S. No.	Symptoms	Day 1		Day 75	
		Control	Treatment	Control	Treatment
1.	Chest tightness	65	70	50	33
2.	Cough	54	37	33	8
3.	Breathlessness	54	57	29	14
4.	Chest pain	14	9	6	2
5.	Wheeze	69	65	58	24
6.	Nocturnal symptoms	42	49	29	10
7.	Miscellaneous	6	4	4	2

Table 5: Number of asthma attack more than 2 per week in percentage

Group	Number of asthma attack more than 2 per week			
	Day 1		Day 75	
	N	%	N	%
Control	34	65	18	35
Treatment	37	72	10	19

Table 6: Number of times using asthma rescue drug per week

Group	Number of times using asthma rescue drug per week			
	Day 15		Day 75	
	N	%	N	%
Control	25	49	13	25
Treatment	23	45	5	10

Table 7: Asthma triggering factors in percentage

S. No.	Factors	Control		Treatment	
		n	%	*n*	%
1.	Exercise	18	35	21	41
2.	Exposure to cold	45	87	40	78
3.	Smoking	32	62	39	76
4.	Dust	48	92	43	84
5.	Emotional factors	12	23	10	19
6.	Animal dander	9	17	14	27
7.	Mosquito repellents	6	12	2	4
8.	Irritants and smoke	18	35	24	47
9.	Drugs	4	8	2	4
10.	Food and food additives	18	35	21	41
11.	Chemicals	14	27	19	37
12.	Miscellaneous	5	10	7	14

Table 8: Mean and standard deviation in PEFR

Diagnostic parameter	Group	N	Mean±S.D
PEFR	Control	52	56.73±67.409
	Treatment	51	99.41±62.142

Significance level $p > 0.001$

Patient who had shown 12% improvement in FEV_1 from baseline value was higher percentage in montelukast-treated group. The increase in asthma-free days and decrease in asthma symptoms

Table 9: Mean and standard deviation in FEV_1

Diagnostic parameters	Groups	*n*	Mean±S.D
FEV_1	Control	52	6.46±9.539
	Treatment	51	9.51±7.030

Significance level $P>0.05$

Table 10: Improvement in FEV_1

Group	Male		Female		Total
	n	%	*n*	%	
Control	5	10	7	14	12
Treatment	12	24	10	20	22

Significance level $P > 0.05$

Table 11: Smoking status in percentage

Smoking status	Groups	
	Control %	Treatment %
Non-smokers	59	60
Smokers	25	24
Former smokers	21	16

indicate improvement in the control of asthmatic inflammation due to the action of montelukast.

The increase in the PEFR in the montelukast-treated group was observed which indicates the improvement in the lung function. Both groups have improvement in PEFR values, but significant improvement was observed in the montelukast-treated group only. Pulmonary function test parameter FEV_1 did not have such a significant improvement in both groups. However, 12% improvement in FEV_1 from the baseline has shown higher rate in the montelukast-treated group (43%), whereas the budesonide-treated group has shown a less improvement (23%).

Previous montelukast studies using PEFR as a primary parameter have shown the progressive improvement in asthma control (Price *et al.*, 2003). Mean morning peak expiratory flow rate (AM PEFR) improved in 10 weeks of treatment. During the treatment days, the change in AM PEFR from the baseline was significantly greater in montelukast 10 mg + budesonide 800 mg group than in double dose budesonide 1600 mg group ($P < 0.001$), indicating faster onset of action in the montelukast group. Furthermore, improvement has observed in montelukast groups in terms of mean daytime symptom score, nocturnal awakening, exacerbations, asthma free days, peripheral eosinophil count, and asthma-specific quality of life.

The present study has achieved a significant control of asthma, evidenced by a low percentage of asthma exacerbation as 35% in the budesonide group and 19% in the montelukast group and progressive reduction in use of asthma rescue drug as 25% and 13% in the budesonide and montelukast groups, respectively. Reduction in asthma symptoms was more observed in montelukast-treated group than the double dose budesonide group. Patients with persistent asthma attack generally managed by increased dose of inhaled corticosteroid or add-on therapy with a second therapeutic agent. However, increasing the dose of inhaled corticosteroid may produce number of potential side effects.[9] Higher dose of inhaled corticosteroid

may not necessarily result in adequate control of asthma symptoms for all patients.[14] International guidelines suggest that the inhaled corticosteroid dose should be reduced whenever possible.[10] The addition of a second agent with sufficient asthma controlling power may, therefore, useful. The finding of this study suggests that the addition of montelukast to the inhaled corticosteroid promotes a comparable asthma control to doubling the dose of inhaled corticosteroid with enhanced onset of action and lesser potential adverse effects.

A major limitation of this study was the use of different machines for measuring the pulmonary function test, thereby variation has been noticed in the value of FEV_1. However, same peak flow meter was used to measure the PEFR for the entire study, hence, instrumental fluctuation was minimized in measuring the same.[11]

Thus, the use of inhaled corticosteroids is considered as one of the best treatment options for patients with mild-to-moderate asthma conditions. Montelukast is a potent antagonist of cysteinyl leukotrienes and represents the first category of drugs that target this inflammatory pathway in asthma. Montelukast as monotherapy is a good alternative to inhaled corticosteroids (ICSs) for a minority of patients who respond poorly to ICS.[12] Added to ICS, montelukast increases the long-term control of asthma in patients with moderate-to-severe asthma, with some ICS-sparing effect. The safety profile of montelukast is very good, with no confirmation of the suspected increase in the risk of Churg-Strauss syndrome or suicide.[13,14]

CONCLUSION

Pharmacotherapy is essential for asthma management and is based on stepwise treatment for different levels of asthma severity: Intermittent, mild persistent, moderate persistent, and the severe persistent. Common antiasthmatic medications include corticosteroids (inhalation and oral), long-acting beta2-agonists (LABA), cromolyn sodium or nedocromil sodium, methylxanthines, and leukotriene modifiers (LT-M). The use of ICS is considered as one of the best treatment options for patients with mild-to-moderate asthma condition. Anti-inflammatory action of ICS in the lungs is well established and ICS has proven its efficacy in improving pulmonary function and reducing exacerbations of asthma. However, increasing the dose of inhaled corticosteroid may produce number of potential side effects. The cysteinyl leukotrienes, especially LTC_4, LTD_4, and LTE_4, induce many pathological changes in lungs including airflow obstruction, mucus secretion, and inflammatory cell infiltration. Thus, anti-leukotriene agents have beneficial action.

The study demonstrated that montelukast provided as important effect on bronchial responsiveness in patients with mild-to-moderate persistent asthma. Montelukast may offer clinical benefits due to a better compliance and the advantage of reducing the dose of ICS while maintaining symptom control, thus minimizing possible ICS adverse effects.

From the present study, the observation clearly demonstrated for the improvement in asthma control which was evident by peak expiratory flow rate (PEFR), 12% improvement in FEV_1 and asthma symptoms, reduction in asthma exacerbations, as well as decrease in the rate of use of asthma rescue drug.

It is concluded that the addition of montelukast 10 mg to the inhaled budesonide is an effective and alternative treatment to reduce asthmatic attack or severity. At present, it may be useful therapy to control asthmatic attack in adult patients as compare to alone treatment with budesonide.

In future, the present study can be further continued with higher sample size and using same PFT instrument for all patients. We can prefer peripheral eosinophil count as parameter and bronchoprovocation test for the further study.

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