Original Article

Comparative Study of add-on Therapies, Salmeterol and Montelukast to Inhaled Corticosteroids in Mild to Moderate Asthmatic Patients

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ABSTRACT

Objective: The aim of this study was to compare the effect of both add-on therapies; Salmeterol plus Inhaled Corticosteroid and Montelukast and Inhaled Corticosteroid on asthma control in poorly controlled asthma.

Study Design: Randomized clinical trial.

Place and Duration of Study: Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Post-graduate Medical Centre, Karachi from December 2007 to June 2008.

Materials and Methods: 75 patients aged between 15-65 years, suffering from mild to moderate asthma were randomly divided in three groups. Group A was given Salmeterol 50µg and Fluticasone propionate 250µg twice daily, Group B was given tablet Montelukast 10mg at night in addition to Beclomethasone Dipropionate 500µg twice daily and Group C was given Beclomethasone Dipropionate 500µg twice daily. Improvements in Peak Expiratory Flow Rate (PEFR) and FEV_1 were assessed by Peak Expiratory Flow Meter and Spirometry, fortnightly at the beginning and end of treatment respectively. Student paired t test was applied to analyze data.

Results: An improvement of 46.58 %(P-value <0.001), 38.59% (P-value <0.005) and 21.2% (P-*value* not significant) in PEFR was noted in Group A, B and C respectively. In Group A and B FEV_1 increased from1.17L/min (±0.12) to 1.41L/min (±0.13), and 1.42L/min (±0.13) to 1.62L/min (±0.13) respectively, while in Group C it was from 1.24L/min (±0.12) to 1.26L/min (±0.13).

Conclusion: Salmeterol is slightly more effective than Montelukast as add-on treatment in increasing PEFR in patients suffering from mild to moderate persistent asthma.

Key Words: Salmeterol, Montelukast, Inhaled Cortcosteroids(IC), Peak Expiratory Flow Rate (PEFR).

INTRODUCTION

Asthma is a growing public health problem in many countries around the world. Asthma current affects approximately 300 million individuals worldwide and remains a global respiratory health concern[1]. Asthma is an inflammatory disease of the airways associated with intermittent episodes of bronchospasm[2]. Unfortunately, regardless of disease severity, patients have a tendency to underestimate their level of asthma control, and many patients with asthma live with significant symptoms and restrictions. Asthma is a chronic potentially life-threatening condition that is increasing in both prevalence and severity. In mild-to-moderate asthma, there is persistent bronchial inflammation involving primarily lymphocytic and eosinophilic infiltration associated with remodeling of the airway wall[3]. Airway obstruction can lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning[4].

For optimal management, patients with persistent asthma require daily controller therapy. According to the NIH guidelines, inhaled corticosteroids (ICSs) are the most effective anti-inflammatory medications available. Inhaled corticosteroids have been shown to reduce symptoms, reduce risk of hospitalizations for asthma, reduce deaths from asthma, improve lung function, and improve or prevent several of the pathologic alterations associated with airway remodeling[5].

Many patients do not have adequate symptom control while receiving low-dose inhaled corticosteroid treatment and additional second-line therapy is necessary. Combining a long-acting β_2-agonist with low-dose inhaled corticosteroid has been shown to provide equivalent or superior asthma control than using higher doses of inhaled corticosteroid alone, as is reflected in current asthma management guidelines[6].

The introduction of inhaled long-acting inhaled β_2-adrenoceptor agonists (LABAs; Salmeterol and Formoterol) represented an important advance in asthma therapy. Treatment with LABAs provides better

control of symptoms and lung function than short-acting β_2- agonists[7,8].

Several studies show that the combined use of long-acting β_2-agonists with low-to-moderate doses of inhaled corticosteroid therapy appears to provide greater clinical benefit than further increasing the dose of inhaled corticosteroid[9].

In fact, when combined with moderate doses of inhaled glucocorticosteroids, these drugs have been shown to improve symptoms and lung function more effectively than doubling the dose of inhaled corticosteroids[10] .

Leukotriene receptor antagonists (LTRA) are a novel class of therapy available in the management of asthma. They have both anti-inflammatory and bronchodilator activity, although not as great as that of inhaled corticosteroids or long-acting β_2-agonists, respectively[11].

Montelukast is a potent, specific LTRA. Administered once daily in tablet form, Montelukast reduces the signs and symptoms of persistent asthma in children as young as 2 years of age[6]. While the improvements in FEV_1 are modest (6 to 10%), asthma symptoms and quality of life appear to be improved to a greater degree with Montelukast administration than is FEV_1[12,13]. There has been speculation about whether symptom improvement with the systemic delivery of Montelukast could be due to systemic effects on both the small and large airways[14] .

As long-acting β_2-agonist and leukotriene antagonists act on the different parts of inflammatory cascade, aim of this study was to compare the effect of both add-on therapies; Salmeterol plus ICS and Montelukast and ICS on asthma symptoms and Peak expiratory flow rate (PEFR).

MATERIALS AND METHODS

Study Design: This was a randomized, open-label, parallel group study carried out at the department of Pharmacology and Therapeutics, BMSI, in collaboration with Department of Chest Medicine, JPMC, Karachi. The ethical committee of this institution approved the study protocol.

Patients: A total of 75 mild to moderate asthmatic, male and female patients were recruited in the study. These patients aged between 15-70 years were receiving ICS therapy for asthma. Patients were excluded from study if: they were taking systemic steroids or have taken systemic steroids in past 6 months; have had respiratory infections and taken antibiotics in past 4 weeks. Patients suffering from diabetes, heart disease, hypertension, hepatic and renal diseases were also excluded from study.

Study Procedure: The study extended over 12 weeks period which was preceded by 2 weeks run-in period. Subjects were assessed in run-in period to determine eligibility for randomization based on pre-specified criteria i.e patients of either sex suffering from mild to moderate persistent asthma not controlled by ICS. During treatment period patients were randomized to either Group A, given Salmeterol 25µg/Fluticasone 125µg inhaler (Salmicort), two puffs twice daily; Group B, given Tab. Montelukast 10mg (Ventec) at night along with Beclomethasone Dipropionate inhaler 250µg (Beckson Forte) two puffs B.D. or Group C, given Beclomethasone Dipropionate inhaler, 250µg, two puffs B.D. for 12 weeks with follow up visits fortnightly.

Peak expiratory flow rate (PEFR) was measured by Micropeak. Peak flow meter. Reg. Design no. 2100423, Made in UK, on every clinical visit and recorded. The safety and tolerability of Salmeterol and Montelukast was assessed by monitoring adverse events (including exacerbation of asthma) blood pressure and heart rate at clinic visits throughout the study.

Statistical Analysis: All the values are taken as mean ±SEM. The primary efficacy measurement was the change in the PEFR fortnightly throughout the study period from baseline to end point. Student pair test was used to analyze the data.

RESULTS

Patients: Of 100 patients enrolled in study 75 were randomized to treatment, 25 in each treatment group. Five patients withdrew during treatment period. One patient withdrew from Salmeterol group two patients each from Montelukast and ICS groups because of non-compliance. Demographic data and baseline PEFR are given in Table-1. Patients in all three groups were matched for age, sex and type of asthma they were suffering from. Male to female ratio was same as observed in international studies i.e. 25:75 in all groups.

Peak Expiratory Flow Rate: Both add-on therapies, Salmeterol and Montelukast significantly improve PEFR, after each fortnight treatment while patients of ICS group showed non significant improvement in PEFR, as shown in Table-2.

By week 12 in Group A patients (Salmeterol plus ICS), improvement in PEFR was from 189.4 L/min (±16.12) to 354.58 L/min (±7.61) which is 46.58% as compared to baseline value, while in Group B (Montelukast plus ICS), improvement of 38.59% in PEFR from 201.3 L/min (±14.72) to 327.82 L/min (±12.41) was observed as compared to baseline value. Whereas in Group C (ICS), PEFR improved to only 21.2% from 182.60 L/min (±17.05) to 231.73 L/min (±13.84) in comparison to baseline observation as shown in Figure 1.

Spirometry: Improvement in Spirometric values from baseline to end of study was significant in Group A, Group B and non-significant in Group C patients. In Group A and in Group B, FEV_1 increased

from1.17L/min (±0.12) to 1.41L/min (±0.13), and 1.42L/min (±0.13) to 1.62L/min (±0.13) respectively, while in Group C it was from1.24L/min (±0.12) to 1.26L/min (±0.13). FEV_1/FVC improved from 67.75 (±2.84) to 83.14(±1.58), and 73.84 (±2.61) to 87.81(±1.7) in Group A and B respectively while in Group C it was from 68.27(±2.88) to 69.95 (±2.88) as shown in Table 3.

Table No.1: Demographic and Baseline Characteristics of Patients

Characteristics	GROUP A (Salmeterol plus Inhaled Corticosteroid)	GROUP B (Montelukast plus Inhaled Corticosteroid)	GROUP C (Inhaled Corticosteroid)
Total Patients	25	25	25
Remained in study	24 (96%)	23 (92%)	23 (92%)
Left out	01 (4%)	02 (8%)	02 (8%)
Age			
Mean	34	36	35
Range	15-65	15-65	15-65
Gender			
Male	6 (25%)	6 (26%)	6 (26%)
Female	18 (75%)	17 (66.6%)	17 (66.6%)
Type of Asthma			
Mild	13 (54.1%)	12 (52.1%)	12 (52.1%)
Moderate	11 (45.8%)	11 (47.8%)	11 (47.8%)
Family History			
Positive	19 (79.1%)	19 (82.6%)	18 (78.2%)
Negative	5 (20.8%)	4 (17.3%)	5 (21.7%)
Spirometry			
FVC L/min	1.7 (±0.145)	1.88 (±0.158)	1.70 (±0.14)
FEV1 L/min	1.2 (±0.128)	1.41 (±0.134)	1.20 (±0.12)
FEV1/FVC	68.55 (±2.84)	73.61 (±2.61)	68.37 (±2.8)
PEFR L/min	189.4 (±16.4)	201.3 (±14.72)	189.8 (±17.0)

Values are expressed in Mean (±SEM) (Percentage)
SEM: Standard Error of Mean
FVC: Forced Vital Capacity
FEV_1: Forced Expiratory Volume in First Second
PEFR: Peak Expiratory Flow Rate L/min: Liters per minute

Table No.2: Improvement In Peak Expiratory Flow Rate Among All Groups From Day 0-90

Groups	Day 0		Day 90		Percentage change	P-value
Group A	189.4 L/min	(±16.12)	354.58 L/min	(±7.61)	46.58%	<0.001***
Group B	201.3 L/min	(±14.72)	327.82 L/min	(±12.41)	38.59%	<0.005**
Group C	182.60 L/min	(±17.05)	231.73 L/min	(±13.84)	21.2%	N.S
Group A versus Group B						N.S
Group A versus Group C						<0.001***

Values are expressed in Mean (±SEM)
SEM: Standard Error of Mean
P-value: Probability value
***: Highly Significant
**: Moderately Significant
N.S: Not Significant

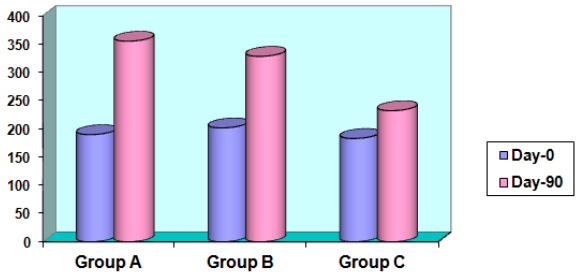

Figure No.1: Comparison of Peak Expiratory Flow Rate among all groups from day 0-90

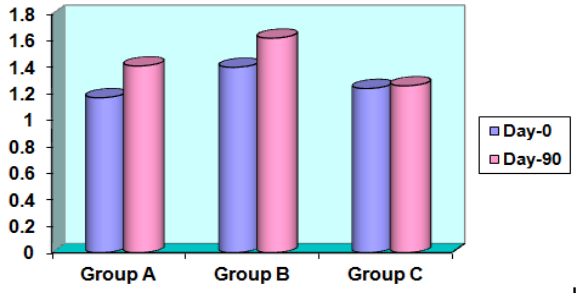

Figure No.2: Comparison of FEV1 among all groups from day 0-90

Safety: Both add-on treatments are well tolerated by patients. Side effects reported by patients were mild and did not require cessation of therapy.

Table No.3: Comparison of Spirometry in All Three Groups from Day 0-90

GROUPS	Spirometry	Day-0		Day-90		P-value
GROUP A	FEV_1 L/min	1.17	(±0.128)	1.41	(±0.133)	<0.001***
	FEV_1/FVC	67.75	(±2.84)	83.14	(±1.58)	<0.005**
GROUP B	FEV_1 L/min	1.40	(±0.13)	1.62	(±0.133)	<0.005**
	FEV_1/FVC	73.84	(±2.61)	87.21	(±1.7)	<0.01*
GROUP C	FEV_1 L/min	1.24	(±0.12)	1.26	(±0.13)	N.S.
	FEV_1/FVC	68.27	(±2.88)	69.95	(±2.82)	N.S.

Values are expressed in Mean (±SEM) P-value: Probability value SEM: Standard Error of Mean
***: Highly Significant FEV_1: Forced expiratory volume in First Second **: Moderately Significant
FVC: Forced Vital Capacity *: Significant N.S: Not Significant L/min: Liters per minute

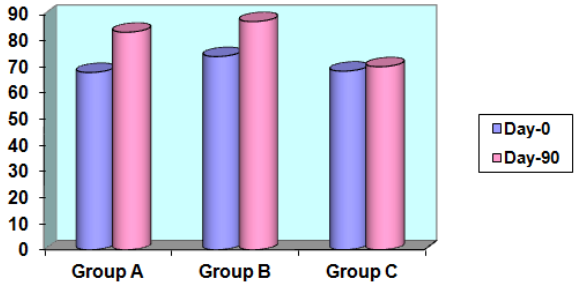

Figure No.3: Comparison of FEV1/FVC among all groups from day 0-90

DISCUSSION

Substantial variations in asthma outcomes persist despite the development and dissemination of national and international guidelines for the diagnosis and management of asthma[15].

Our study is the comparative study regarding the treatment options for patients with symptomatic asthma, despite taking low dose inhaled corticosteroids. Our aim was to evaluate the effectiveness of these treatments in clinically realistic situation with clinically relevant outcomes. Overall, the benefit provided by each add-on treatment on PEFR and spirometric values was significant in both treatment groups (group A and group B) recorded fortnightly and at the start and end of study respectively.

Adding a leukotriene modifier to ICS versus using SAL with an ICS has been evaluated in several randomized clinical trials. These trials have demonstrated greater efficacy of using SAL with an ICS compared with either Zafirlukast or Montelukast as add-on therapy to ICSs in patients with persistent asthma.

The present trial demonstrates that adding Salmeterol or Montelukast provided more benefit than ICS alone as evident by improvement in PEFR. Moreover, Salmeterol/ICS combination has shown more increase in PEFR as compared to Montelukast/ICS, 165.18L/min and 126.5L/min respectively. These results are consistent with the result of Cochrane review[16] which suggested superiority for the long-acting β_2-agonist and ICS combination over the combination of a leukotriene receptor antagonist and an ICS, with significantly greater improvements in lung function, symptom control and quality of life[16].

Busse and coworkers observed that improvement in morning PEF more than doubled in patients using SAL (29.6L/min) when compared with patients receiving zafirlukast (13.0 L/min; P<0.001) [17]. In a clinical trial by Nelson and associates, it was evident that patients treated with the combined FP and SAL had greater overall asthma control with significantly greater improvements in morning and evening PEF (P<0.001), FEV_1 (P<0.001), rescue-free days (P<0.032), and shortness of breath symptom scores (P<0.017) compared with patients receiving FP plus montelukast[18].

A clinical trial done by Bjermer and co-workers supports our study, as patients receiving salmeterol and fluticasone had a significantly larger increase in morning peak expiratory flow (litres per minute) compared with patients receiving montelukast and fluticasone (least squares mean (SE) change from baseline of 34.59 (1.70) versus 17.73 (1.69), P < 0.001). Both treatments significantly improved peak expiratory flow over baseline values (P < 0.001)[19].

Comparing combination of Salmeterol and ICS with ICS alone, this study is in line with trial conducted by Bergmann et al, which showed that combined Salmeterol Fluticasone (SFC) therapy resulted in significantly greater improvements in PEFR and symptom control than doubling the dose of FP. At week 12, morning PEFR had increased by 52 L/min from baseline in patients on SFC and by 36 L/min in subjects receiving FP. The adjusted difference between groups was 16.6 L/min (95% confidence interval, 1.1 to 32.0 L/min)[20] .

Pavord et al in 2007 conducted a similar study comparing the same treatment groups as we did in this study and found Salmeterol plus ICS led to better symptom control and improvement in lung function than the Montelukast plus ICS combination with

significantly more rescue medication-free nights and greater increases relative to baseline in morning and evening PEF [21] same results seen in our study.

CONCLUSION

In this study, we have shown that the Salmeterol and Montelukast are both effective in improving PEFR (Salmeterol is a better than Montelukast) when given in addition to inhaled corticosteroids. Longer-term studies are required to evaluate the effects of Salmeterol and Montelukast on asthma control and exacerbation rates when administered as second-line therapy in addition to inhaled corticosteroids.

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