

## Formoterol versus montelukast as add on therapy to low dose budesonide in persistent asthma: effect on lung function

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### ABSTRACT

**Background:** Choice between LABAs and LTRAs as add on drugs to low dose ICS in persistent asthma remains unclear due to limited data on the comparative efficacy of these two groups of drugs. The aim of this study was to compare the effects of formoterol and montelukast on lung function, when added to low dose Budesonide in persistent asthma.

**Methods:** This was an institution based randomized open label study. 72 asthmatics satisfying selection criteria of the study were randomized to receive either inhaled budesonide and formoterol (FB group) or inhaled budesonide and oral montelukast (MB group) for 12 weeks. PEF value at end point was primary efficacy measure. Secondary efficacy measures were PEF values measured at the end of 1, 4 and 8 weeks and the end point value of FEV1.

**Results:** Both the groups showed significant improvement in the lung function tests. However inter-group comparison showed that PEF value at end point of FB group was significantly greater than that of MB group (81.94% vs 63.82%,  $p < 0.05$ ). Notable observation was that the superiority of the FB group with respect to PEF values was maintained from the first week itself. FB group also had significantly better results than MB group for FEV1 (67.88% vs 64.88%,  $p < 0.05$ ).

**Conclusions:** In the present study, formoterol was found to be superior to montelukast in improving lung function when added to low dose budesonide in persistent asthma.

**Keywords:** Budesonide, Formoterol, Lung function, Montelukast

### INTRODUCTION

Inhaled corticosteroids (ICS) represent the most effective controller medications in persistent asthma. In patients who are not controlled by low dose ICS alone, Global Initiative for Asthma (GINA) guidelines recommend either escalating the dose of inhaled corticosteroids (ICS) or the addition of a second controller drug in the form of long acting beta 2 agonist (LABA) or leukotriene receptor antagonist (LTRA) to low dose ICS. Due to side effects at higher doses of ICS, the option of adding a second controller drug to low dose ICS is preferred.<sup>1</sup> However, LABAs and LTRAs are characterized by markedly

different pharmacologic properties that can bring about different effects on the basic mechanisms of the disease.<sup>2,3</sup> Also the data available on the comparative efficacy of these two groups of drugs is largely contrasting. Hence, in this study we compared the effects of a LABA like formoterol and an LTRA like montelukast on lung function, when added to low dose ICS like budesonide in persistent asthma.

### METHODS

This randomized open label comparative study was conducted at a tertiary centre in Kerala after getting ethical clearance from the Institutional Ethics committee. Authors

included 72 subjects recruited from the outpatient department of Pulmonology. Male and female asthmatics aged between 18 to 60 years of age whose asthma was inadequately controlled despite receiving regular low dose inhaled Budesonide (i.e. at a dose of 400µg/day) for at least 6 weeks prior to screening, were eligible for inclusion in the study. Asthma control in patients was considered inadequate if their lung function i.e. Peak expiratory flow (PEF) or Forced expiratory volume at the end of 1<sup>st</sup> second (FEV<sub>1</sub>) before administration of a bronchodilator was less than 80% of the predicted value on the day of randomization.<sup>1</sup> Pregnant and lactating women, smokers, patients with accompanying respiratory tract infections, patients who received treatment with oral steroids/mast cell stabilizers/ LTRAs/ LABAs or oral short acting beta 2 agonists in the month preceding the screening and patients with history of hypertension/diabetes/heart disease or other co-morbid conditions requiring concurrent medications were not included in the study. Patients whose (PEF or FEV<sub>1</sub>) was less than 80% of the predicted value on the day of screening entered a 2 week run in period during which period they used 200µg Budesonide twice daily through a metered dose inhaler. After the run in period, patients who satisfied the aforesaid inclusion criteria on the day of randomization were enrolled in the study after obtaining written informed consent. The enrolled patients were randomly divided into two groups using the block randomization technique. Both the groups were treated for 12 weeks. The first intervention group (FB group) was prescribed a combination of inhaled Budesonide and Formoterol (200µg +6µg/puff), one puff twice daily through a metered dose inhaler and the second intervention group (MB group) was prescribed inhaled Budesonide (200µg/puff), one puff twice daily through a metered dose inhaler and an oral dose of Montelukast (10mg) in the evening.<sup>4,5</sup> Patient compliance was assured by asking them to bring empty packages of medicines and also from the history. Patients who developed severe asthma exacerbations requiring an unscheduled visit to the doctor, emergency room, hospital admission or treatment beyond the drugs included in the study were withdrawn from the study. The efficacy parameters were recorded at baseline (i.e. at randomization) and at the follow up visits scheduled at the end of 1, 4, 8 and 12 weeks by spirometry. In this study, the pre-specified primary efficacy measure was PEF measured at 12 weeks. PEF values measured at the end of 1 week, 4 weeks and 8 weeks and the end point values of FEV<sub>1</sub> were considered as secondary efficacy measures. Patients who completed the entire 12 weeks of treatment period were included in the statistical analysis. Statistical analysis was done by applying t test and estimating 'p' value using Statistical package for social service (SPSS) software. The p value of less than 0.05 was considered statistically significant.

## RESULTS

After screening assessment and 2 weeks run in period, 72 patients were randomized into 2 groups of 36 each to receive either of the treatments for 12 weeks. There were

2 drop outs from each group. 68 patients satisfactorily completed the treatment period and were included in the main analysis.

Authors compared the mean values of the efficacy parameters of the study groups at baseline using Independent t test (Table 1) and found them to be comparable (p value of each parameter being more than 0.05).

**Table 1: Baseline comparison of efficacy parameters of the study groups (Independent t test).**

Efficacy parameter	Group	Mean	SD	t	p Value
PEF (% predicted)	FB group	61.88	4.816	-0.915	0.363
	MB group	63.47	4.919		
FEV <sub>1</sub> (% predicted)	FB group	56.88	3.427	-1.921	0.059
	MB group	59.12	5.856		

Authors compared the baseline and end point values of PEF and FEV<sub>1</sub> in each of the groups to assess the improvement in each group. Both the groups showed significant increase in the PEF and FEV<sub>1</sub> values (Tables 2 and 3).

**Table 2: Comparison of baseline and end point values of efficacy parameters of FB group (paired t test).**

Efficacy parameter	Mean	SD	t	p value	
PEF(% predicted)	Baseline	20.06	0.78	25.69	<0.00001
	End point				
FEV <sub>1</sub> (% predicted)	Baseline	11.00	0.13	82.39	<0.00001
	End point				

**Table 3: Comparison of baseline and end point values of efficacy parameters of MB group (paired t test).**

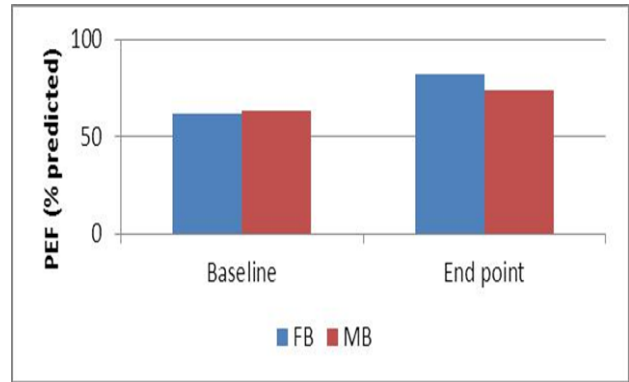
Efficacy parameter	Mean	SD	t	p value	
PEF(% predicted)	Baseline	10.82	0.45	23.96	<0.00001
	End point				
FEV <sub>1</sub> (% predicted)	Baseline	05.56	0.17	32.72	<0.00001
	End point				

Authors compared the primary efficacy measure (PEF at end point) of the two groups using Independent t test. At the end point, mean values of PEF of both the groups increased, reaching 81.94% in the FB group and 73.82% in the MB group but the mean value of FB group was

significantly higher than that of MB group ( $p < 0.05$ ) (Table 4 and Figure 1).

**Table 4: Inter group comparison of primary efficacy measure (Independent t test).**

Primary efficacy measure	Group	Mean	SD	t	p value
PEF (% predicted) at end point	FB group	81.94	1.705	10.498	0.000
	MB group	73.82	4.174		



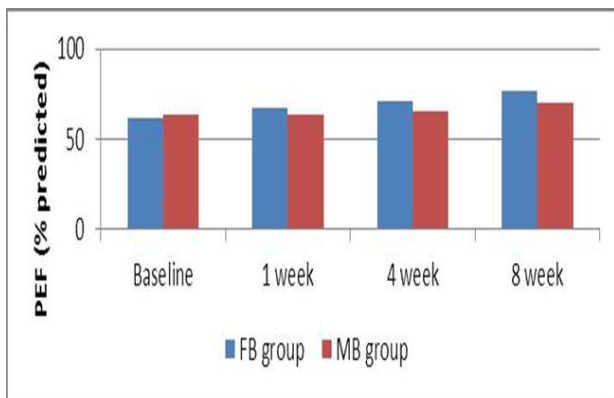
**Figure 1: Comparison of mean values of PEF of the study groups at baseline and end point.**

**Table 5: Inter group comparison of secondary efficacy measures (Independent t test).**

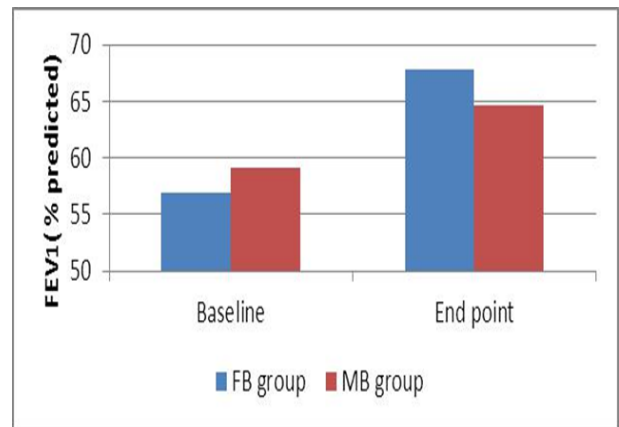
Secondary efficacy measure	Group	Mean	SD	t	p value
PEF (% predicted) at end of 1 week	FB group	67.74	3.662	4.055	0.000
	MB group	63.47	4.919		
PEF (% predicted) at end of 4 weeks	FB group	70.85	2.956	5.771	0.000
	MB group	65.53	4.494		
PEF (% predicted) at end of 8 weeks	FB group	76.82	2.236	8.603	0.000
	MB group	69.65	4.320		
FEV <sub>1</sub> (% predicted) at end point	FB group	67.88	3.255	2.825	0.006
	MB group	64.68	5.762		

The secondary efficacy measures were compared in a similar manner. The FB group had significantly better results for each of the secondary efficacy measures (Tables 5, Figure 2 and Figure 3).

Mean values of PEF continued to increase in both the groups from the start of the study till the end point. At all times, the values of FB group were significantly greater than those of the MB group (Figure 4).



**Figure 2: Comparison of mean values of PEF of the study groups at baseline, at the end of 1 week, 4 weeks and 8 weeks.**

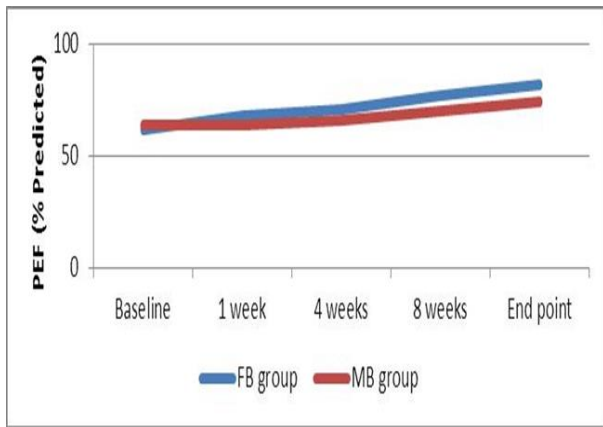


**Figure 3: Comparison of mean values of FEV1 of the study groups at baseline and end point.**

**DISCUSSION**

Asthma is a public health problem affecting 4.3% of the adult population globally.<sup>6</sup> Inhaled corticosteroids (ICS) are the first line controller treatment of persistent asthma. Though low dose ICS are effective in most patients, some remain symptomatic despite the therapy. Treatment in these patients is stepped up by either increasing the dose of inhaled corticosteroids or by adding a concomitant

second drug to supplement the effect of the low dose ICS. As higher doses of ICS are associated with greater adverse effects, the option of adding a concomitant second drug like LABA or LTRA to low dose ICS is recommended by international guidelines.<sup>1</sup>



**Figure 4: Mean values of PEF of the study groups from the start to end of treatment.**

LABAs and LTRAs have been separately compared with placebo and with increased doses of inhaled corticosteroids and many a time been proved to be therapeutically superior or similar.<sup>7-10</sup> However choice between these two groups of drugs is not easy as there is limited data on the comparative efficacy and safety of these two groups of drugs.

Out of the 72 patients enrolled in this study, 68 patients satisfactorily completed the treatment period. This high rate of response can be attributed to the motivation of patients by the investigator and the free supply of medicines.

In this study, both the groups had significant improvement in the PEF and FEV1 values at the end of the study. The data from the present study however is in contrast with that presented by Buchvald et al, and Nelson et al, wherein the group treated with LABA was the only one with significant increase in lung function, whereas the improvement in the lung function of the group treated with LTRA was not significant.<sup>11,12</sup> However, in the study done by Straub et al, add on therapy with montelukast brought about significant improvement in lung function.<sup>13</sup>

As per our study, the FB group showed significantly greater improvement in PEF and FEV1. This is in accordance with studies done by Ringdal et al, Ceylan et al.<sup>14,15</sup> The fact that mean values of PEF of FB group were significantly greater than that of MB group throughout the study period showed that FB treatment was better than MB treatment in improving lung function right from the first week after the start of the respective treatments. This significant superiority of LABA over LTRA in improving PEF at a much earlier point in the course of treatment was

also shown in the 2 week study by Wilson and his colleagues.<sup>16</sup>

A notable finding of this study was that PEF values continued to increase during the course of the 12 week study period in both the groups and that the values did not plateau for either of the groups at the end of 12 weeks (Figure 4). This was in contradiction to the study by Fish et al wherein PEF values reached a plateau for both the groups at the end of 12weeks.<sup>17</sup>

## CONCLUSION

Thus, authors conclude that both formoterol and montelukast bring about significant improvements in lung function when added to low dose budesonide. However, inter- group comparison shows formoterol to be the better therapeutic option than montelukast. The fact that the PEF values for both groups did not plateau at the end of the study period warrants the need for future studies of longer duration to assess whether this treatment related difference persists for a longer period of time.

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