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A RANDOMIZED OPEN LABEL TRIAL TO COMPARE THE EFFICACY AND SAFETY OF FORMOTEROL AND BUDESONIDE WITH THAT OF MONTELUKAST AND BUDESONIDE IN STEP 3 TREATMENT OF ASTHMA

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ABSTRACT

Context: Choice between LABAs and LTRAs as add on drugs to low dose ICS in step 3 treatment of asthma remains unclear due to limited data on the comparative efficacy and safety of these two groups of drugs. **Objectives**: To compare efficacy and safety of Formoterol plus Budesonide with that of Montelukast plus Budesonide in step 3 treatment of asthma. **Settings and design**: Institution based randomized open label study. **Materials and methods**: 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 values of FEV_1, symptom scores, symptom free days/week, night awakenings/week , rescue puffs/week and rescue free days/week. Safety profile of the two treatments were based on adverse effects and laboratory parameters. **Results**: PEF value of FB group was

significantly greater than that of MB group ($p<0.05$). FB group had significantly better results than MB group for FEV_1 ($p<0.05$), total symptom scores ($p<0.05$), wheeze score ($p<0.05$), shortness of breath score ($p<0.05$), chest tightness score ($p<0.05$), night awakenings ($p<0.05$), symptom free days ($p<0.05$), rescue puff use ($p<0.05$) and rescue free days ($p<0.05$). Adverse effects were of similar frequency. **Conclusion**: Formoterol plus Budesonide is the better therapeutic option than Montelukast plus Budesonide for the step 3 treatment of asthma.

KEYWORDS: Asthma control, Budesonide, Formoterol, Montelukast.

INTRODUCTION

Global Initiative for Asthma (GINA) guidelines recommend either high dose inhaled corticosteroids (ICS) or addition of second controller drug in the form of long acting beta2 agonists (LABAs) or leukotriene receptor antagonists (LTRAs) to low dose ICS in step3 treatment of asthma. Due to side effects at higher doses of ICS, the option of adding a second controller drug to low dose ICS is preferred at step3.[1] There is limited data on the direct comparison of LABAs and LTRAs when added to low dose ICS. Therefore, we assessed the better therapeutic option between the two in step3 treatment of asthma.

MATERIALS AND METHODS

This randomized open label comparative study was conducted at our centre from 1st July 2011 to 30th June 2012 after getting ethical clearance from the Institutional Ethics committee. We included 72 subjects recruited from outpatients of Department of Pulmonary Medicine. Male and female asthmatics aged 15-60 years whose asthma was inadequately controlled despite receiving regular low dose inhaled Budesonide (i.e. at a dose of 400µg/day) for atleast 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^{st} second (FEV_1) before administration of a bronchodilator was less than 80% of the predicted value on the day of randomization or if they had one or more of the following in the week preceding the randomization: daytime symptoms more than two times, any limitation of daily activity, any night time awakening or use of more than two rescue puffs.[1] 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. Screening assessment of patients included medical history, physical examination, spirometry and laboratory investigations like complete blood count, random blood sugar, liver function test, renal function test, serum electrolytes and electrocardiogram. Detailed case proformas were developed to collect the data. Patients who gave a history of being symptomatic despite low dose Budesonide for atleast 6 weeks prior to screening and whose lung function (PEF or FEV_1) was less than 80% of the predicted value on the day of screening entered a 2 week run in period to assess their asthma control with respect to symptoms, rescue medicine use, night time awakenings and also to establish the baseline values for these parameters. During the run in period, patients were required to use 200µg Budesonide twice daily through a metered dose inhaler and were asked to take no other medication other than Salbutamol 100µg/puff as rescue medication. 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 (200 µg +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.[2,3] During the treatment period, all patients were asked to take no other medication related to their present condition. However, they were allowed to use Salbutamol 100µg/puff as rescue medication for symptomatic relief as and when needed and were asked to record the number of puffs of Salbutamol used daily. 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. Of these, except for PEF and FEV_1 values which were measured by spirometry on the day of the scheduled visits, all other parameters were assessed, based on the information provided by the patient.

•Values of PEF (%predicted) and FEV_1 (%predicted) measured by spirometry on the day of the visit.

•Symptoms (wheezing, chest tightness, shortness of breath) in the week preceding the day of the scheduled visit were scored using a 5 point Likert scale(0-no symptoms, 1-symptoms present but cause no discomfort, 2-symptoms cause discomfort but do not prevent normal daily activity, 3- symptoms cause discomfort and prevent daily activity of patient for 1 day, 4- symptoms cause discomfort and prevent daily activity of patient for 2 or more days, 5-symptoms cause discomfort and prevent daily activity of patient for the whole week). Individual symptom scores were added up to get the 'total symptom score'.[4]

•Number of symptom free days in the week preceding the day of the scheduled visit.

•Number of night awakenings due to asthma in the week preceding the day of the scheduled visit.

•Number of rescue puffs in the week preceding the day of the scheduled visit.

•Number of rescue medicine free days in the week preceding the day of the scheduled visit.

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 were considered as secondary efficacy measures. The other secondary efficacy measures were the end point values of FEV_1, symptom scores, symptom free days/week, night awakenings/week, rescue puffs/week and rescue free days/week. Physical examination, blood pressure recordings and weight recordings were done at each visit. Patients were also asked to report immediately if they experienced any untoward effect. Adverse effects if any were enquired into and recorded in detail with follow up on the same. Laboratory parameters for assessing safety which included measurements of random blood sugar, liver function tests, renal function tests and serum electrolytes were repeated at the end of 12 weeks. Patients who completed the entire 12 weeks of treatment period were included in the statistical analysis. Statistical analysis was done by applying Chi square test, Independent 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. The process is depicted as a flowchart in Figure 1.

We compared gender distribution of the study groups using Chi square test (Table 1) and found it to be comparable ($p>0.05$) between the groups. The percentage of female patients was higher than male patients in both the groups. Mean age of the patients of the study groups were compared using Independent t test (Table 2) and were found to be comparable ($p>0.05$).

We compared the mean values of the efficacy parameters of the study groups at baseline using Independent t test (Table 3) and found them to be comparable (p value of each parameter being more than 0.05).

We 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 ($p<0.05$). The secondary efficacy measures were compared in a similar manner. The FB group had significantly better results for each of the secondary efficacy measures. Comparison of the primary and secondary efficacy measures of the two groups is shown in Tables 4, 5and Figures 2a – 2i. 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. This is shown in Figure 3.The safety profile of the two treatments were assessed based on adverse effects reported by patients and objective measurements of clinical and haematological parameters as shown in Tables 6, 7 and 8. The adverse effects reported by patients were of similar frequency in both the study groups. On comparing the mean values of clinical and haematological parameters between the groups at baseline and end point using Independent t test, a significant difference was seen in the mean values of SGPT between the study groups at the end point. However, it was unlikely to be the result of the difference in treatment as there was a significant difference in the mean values of SGPT at the baseline measurement itself. Also, the mean values of SGPT at the end point in both the groups were within the normal range. No significant difference was seen between the study groups with respect to other parameters at baseline as well as end point.

Table 1: Comparison of the gender distribution of the study groups.

Group	Gender		p Value
	male	female	
FB group	10(29.4%)	24(70.6%)	
MB group	9(26.5%)	25(73.5%)	0.500

Table 2: Comparison of mean age of the study groups

Group	N	Mean	SD	t	p Value
FB group	34	37.56	5.780	0.936	0.353
MB group	34	36.29	5.357		

Table 3: Baseline comparison of efficacy parameters of the study groups

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_1 (% predicted)	FB group	56.88	3.427	-1.921	0.059
	MB group	59.12	5.856		
Total symptom score	FB group	3.53	1.022	0.462	0.645
	MB group	3.41	1.076		
Wheeze score	FB group	1.06	0.547	0.256	0.799
	MB group	1.03	0.388		
Chest tightness score	FB group	0.94	0.649	-0.198	0.844
	MB group	0.97	0.577		
Shortness of breath score	FB group	1.56	0.504	0.962	0.339
	MB group	1.44	0.504		
Number of symptom free days/week	FB group	0.12	0.478	-0.590	0.557
	MB group	0.21	0.729		
Number of night awakenings/week	FB group	2.06	0.919	-0.244	0.808
	MB group	2.12	1.066		
Number of rescue puffs/week	FB group	4.12	1.175	0.198	0.844
	MB group	4.06	1.278		
Number of rescue free days/week	FB group	2.88	1.175	-0.198	0.844
	MB group	2.94	1.278		

Table 4: Comparison of primary efficacy measure of the study groups.

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		

Table 5: Comparison of secondary efficacy measures of the study groups

Secondary Efficacy measure	Group	Mean	SD	t	p value
PEF (% predicted) at end of 1week	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_1(% predicted) at end point	FB group	67.88	3.255	2.825	0.006
	MB group	64.68	5.762		
Total symptom score at end point	FB group	0.47	0.662	-6.896	0.000
	MB group	2.12	1.225		
Wheeze score at end point	FB group	0.00	0.000		

	MB group	0.18	0.459	-2.224	0.028
Chest tightness score at end point	FB group	0.15	0.359	-6.235	0.000
	MB group	0.82	0.521		
Shortness of breath score at end point	FB group	0.32	0.475	-5.323	0.000
	MB group	1.12	0.729		
Number of symptom free days/week at end point	FB group	5.85	1.500	5.408	0.000
	MB group	3.68	1.804		
Number of night awakenings/week at end point	FB group	0.32	0.589	-2.159	0.035
	MB group	0.65	0.646		
Number of rescue puffs/week at end point	FB group	0.65	1.041	-5.074	0.000
	MB group	2.09	1.288		
Number of rescue free days/week at end point	FB group	6.35	1.041	5.074	0.000
	MB group	4.91	1.288		

Table 6: Adverse effects reported by patients.

Adverse effect	FB group	MB group
Oral candidiasis	1	1
Throat irritation	2	1
Voice problems	1	1

Table 7: Baseline comparison of clinical and laboratory parameters of the study groups

Parameter	Group	Mean	SD	t	p value
SBP (mm of Hg)	FB group	116.18	8.895	-0.146	0.884
	MB group	116.47	7.692		
DBP (mm of Hg)	FB group	76.47	4.750	0.294	0.770
	MB group	76.12	5.514		
Weight (Kg)	FB group	56.85	5.428	0.937	0.352
	MB group	55.65	5.187		
RBS (mg/dl)	FB group	88.21	7.189	-0.462	0.645
	MB group	89.00	6.972		
TB (mg/dl)	FB group	0.729	0.103	-0.123	0.903
	MB group	0.732	0.094		
CB (mg/dl)	FB group	0.088	0.041	1.318	0.192
	MB group	0.077	0.031		
SGOT (IU/L)	FB group	22.44	2.852	-0.930	0.356
	MB group	23.18	3.622		
SGPT (IU/L)	FB group	20.85	3.403	-3.551	0.001
	MB group	24.38	4.691		
BU (mg/dl)	FB group	29.15	3.295	1.929	0.058
	MB group	30.62	2.985		
Creatinine (mg/dl)	FB group	0.885	0.144	-0.287	0.775
	MB group	0.894	0.107		
Serum Na^+ (mEq/L)	FB group	139.91	2.021	-0.290	0.773
	MB group	140.09	2.917		
Serum K^+ (mEq/L)	FB group	4.162	0.313	-1.393	0.168
	MB group	**4.274**	**0.348**		

Abbreviations : SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, RBS-Random Blood Sugar, TB-Total Bilirubin, CB-Conjugated Bilirubin, SGPT- Serum Glutamate Pyruvate Transaminase, SGOT-Serum Glutamate Oxaloacetate Transaminase, BU-Blood Urea, Na^+-Sodium, K^+-Potassium

Table 8: Endpoint comparison of clinical and laboratory parameters of the study groups

Parameter	Group	Mean	SD	t	p value
SBP (mm of Hg)	FB group	116.65	6.637	-0.368	0.714
	MB group	117.24	6.532		
DBP (mm of Hg)	FB group	76.76	4.723	-0.053	0.958
	MB group	76.82	4.407		
Weight (Kg)	FB group	56.90	5.375	0.926	0.358
	MB group	55.71	5.230		
RBS (mg/dl)	FB group	88.00	5.117	-0.843	0.402
	MB group	89.21	6.591		
TB (mg/dl)	FB group	0.735	0.060	0.000	1.000
	MB group	0.735	0.081		
CB (mg/dl)	FB group	0.089	0.040	1.318	0.192
	MB group	0.077	0.031		
SGOT (IU/L)	FB group	22.50	2.620	-0.930	0.356
	MB group	23.21	3.566		
SGPT (IU/L)	FB group	20.97	3.252	-3.517	0.001
	MB group	24.47	4.807		
BU (mg/dl)	FB group	29.15	3.136	-1.992	0.050
	MB group	30.62	2.947		
Creatinine (mg/dl)	FB group	0.885	0.120	-0.864	0.391
	MB group	0.894	0.104		
Serum Na^+ (mEq/L)	FB group	139.91	1.966	-0.189	0.850
	MB group	140.09	3.046		
Serum K^+ (mEq/L)	FB group	4.162	0.295	-1.489	0.141
	MB group	**4.274**	**0.339**		

Abbreviations : SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, RBS-Random Blood Sugar, TB-Total Bilirubin, CB-Conjugated Bilirubin, SGPT- Serum Glutamate Pyruvate Transaminase, SGOT-Serum Glutamate Oxaloacetate Transaminase, BU-Blood Urea, Na+-Sodium, K+-Potassium.

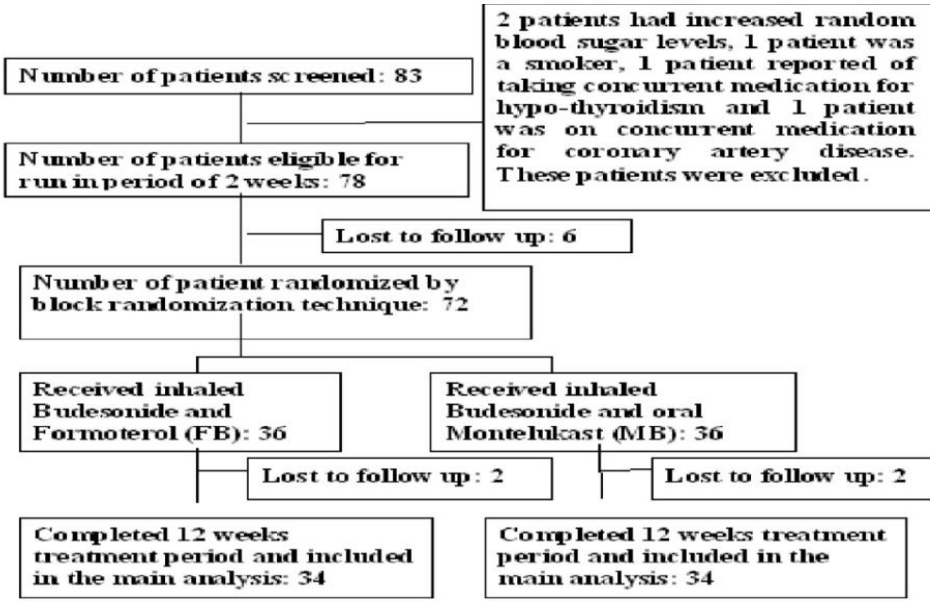

Figure 1: Recruitment, allotment and follow up of study patients

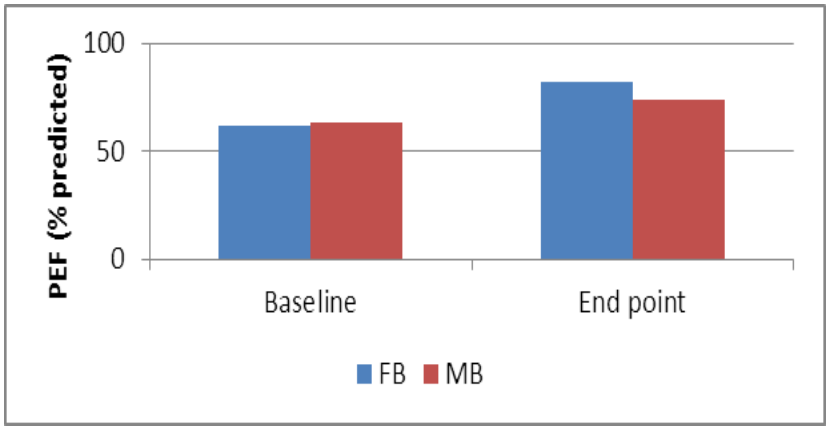

Figure 2a: Comparison of mean values of PEF of the study groups at baseline and end point

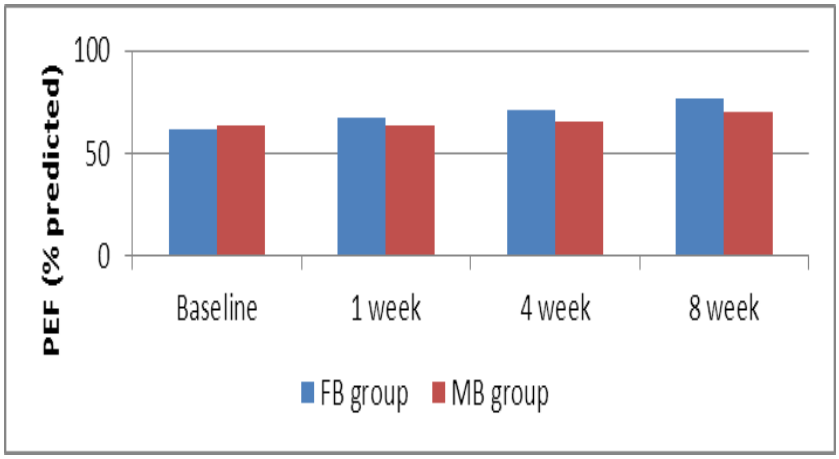

Figure 2b: Comparison of mean values of PEF of the study groups at baseline, at the end of 1week, 4 weeks and 8 weeks.

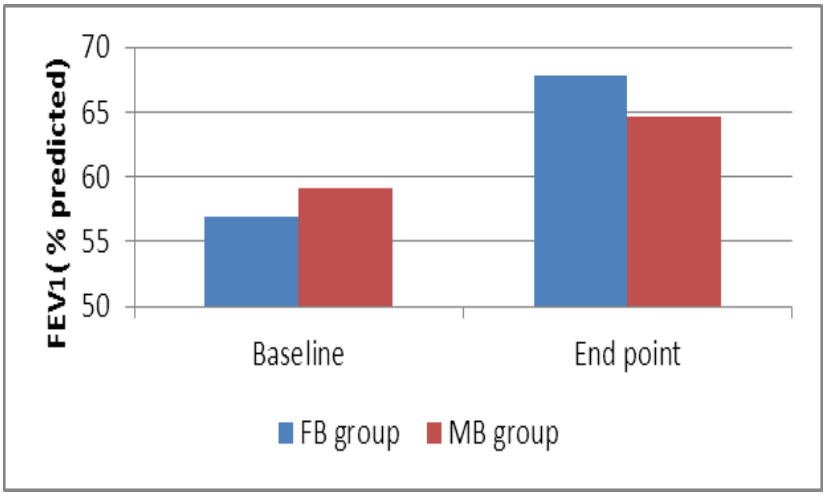

Figure 2c: Comparison of mean values of FEV_1 of the study groups at baseline and end point

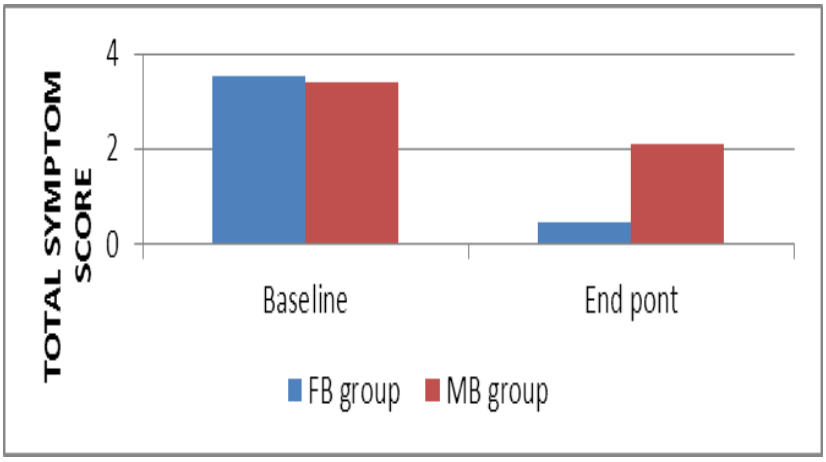

Figure 2d: Comparison of mean values of total symptom score of the study groups at baseline and end point

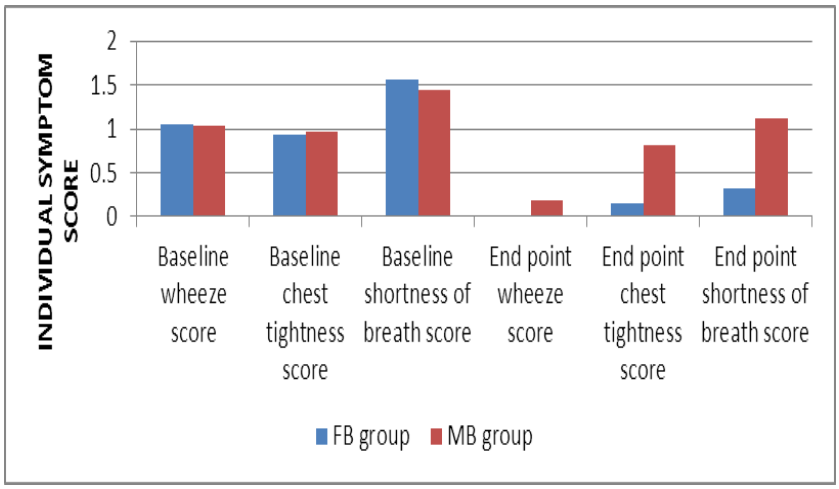

Figure 2e: Comparison of mean values of individual symptom scores of the study groups at baseline and end point

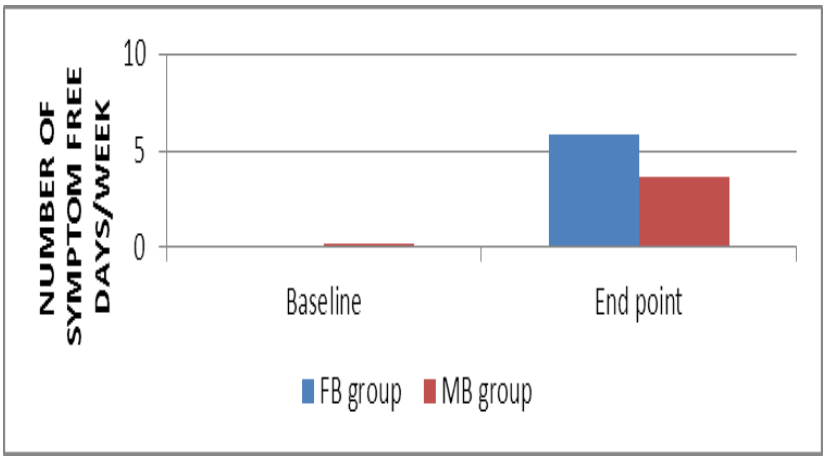

Figure 2f: Comparison of mean values of symptom free days/week of the study groups at baseline and end point.

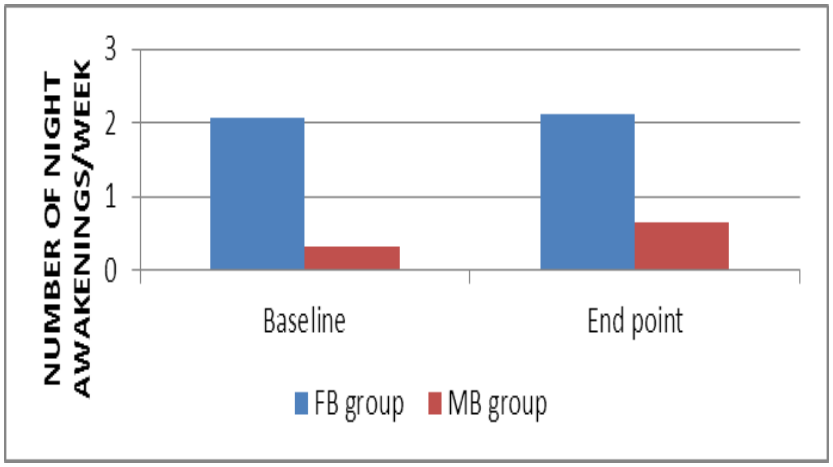

Figure 2g: Comparison of mean values of night awakenings/week of the study groups at baseline and end point

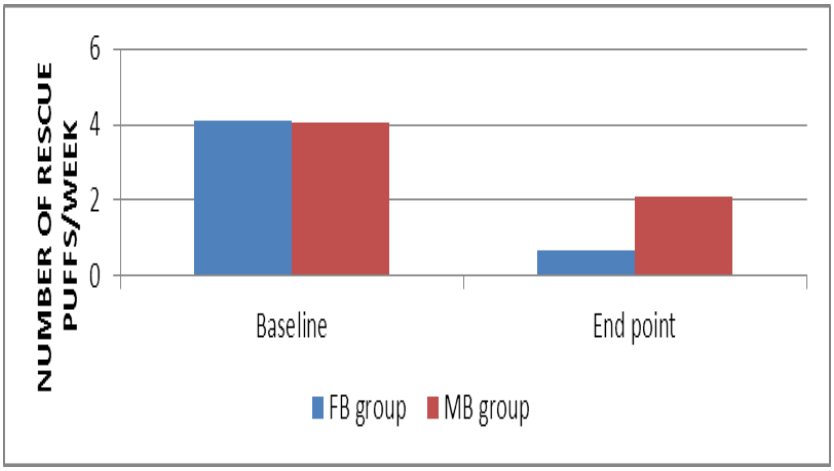

Figure 2h: Comparison of mean values of rescue puffs/week of the study groups at baseline and end point

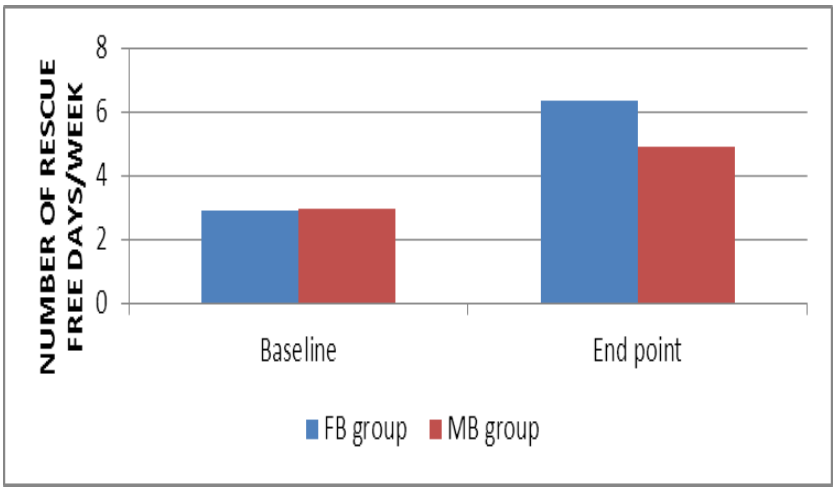

Figure 2i: Comparison of mean values of rescue free days/week of the study groups at baseline and end point

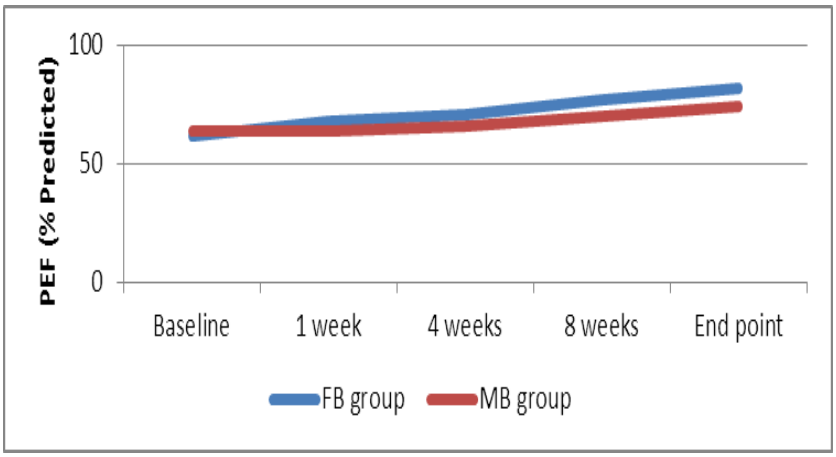

Figure 3: Mean values of PEF of the study groups from the start to end of treatment

DISCUSSION

Asthma is a serious public health problem affecting people of all ages throughout the world. The global prevalence of diagnosed asthma in adults is estimated to be 4.3%.[5] It is a significant burden not only in terms of healthcare costs, but also in terms of loss of productivity and reduced participation in family life. 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 (step 3) 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 to low dose ICS is considered in step 3 treatment of asthma. LABAs and LTRAs have

been recommended by GINA guidelines for use as add on drugs to low dose ICS in step 3 treatment of asthma.[1]

LABAs and LTRAs have been extensively compared with placebo and with increased doses of inhaled corticosteroids and many a time been proved to be therapeutically superior or similar.[6,7,8,9] However choice between these 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 our 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. As per our study, the FB group showed significantly greater improvement in lung function. This is in accordance with studies done by Ringdal et al, Ceylan et al.[10, 11]

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.[12]

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. 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.[13]

FB group was superior to MB group in improving total symptom score as well as individual symptom scores at the end of the study period. However, in the study by Nelson et al, addition of LABA was superior to the addition of LTRA in improving shortness of breath symptom score but there was no significant difference in outcomes such as chest tightness, wheeze and overall symptom scores.[14] Also at the end point, the mean number of night awakenings/week were significantly lower in the FB group than the MB group ($p<0.05$). This was in contrast to the study by Bjermer et al wherein there was no significant difference between the groups in nocturnal awakenings.[15] At the end of treatment, FB group showed significantly better results than MB group with respect to rescue puffs/week and rescue free

days/week. Similar results in rescue medicine use and rescue free days were seen in studies by Ceylan et al, Fish et al.[11, 13]

Both the treatments were well tolerated. The adverse events reported in both the groups were mild and were of similar frequency. None of the adverse effects needed stoppage of medication. The adverse effects reported were throat irritation in two patients in FB group and one patient in the MB group, oral candidiasis in one patient in each group and voice problem in one patient in each group. These were expected side effects of inhaled Budesonide which was common in both the treatments.[16] These were reported during the initial two visits after the start of the treatment. Patients were asked to rinse their mouth after inhalation and advised to use a spacer. Clinical and haematological parameters did not show any significant change from baseline in both the groups. Hence, it can be said that the safety profiles of both the study groups were comparable.

CONCLUSION

Thus we conclude that Formoterol plus Budesonide is the better therapeutic option than Montelukast plus Budesonide for the step 3 treatment of asthma. But the limitation in our study is that it was performed in a single centre. Due to this, size of the patient groups and the duration of the study are low. Further studies of longer duration and in larger number of patients are needed to assess whether these treatment related differences persist for a longer period of time and whether a LABA like Formoterol or a LTRA like Montelukast has a bearing on the natural history of asthma.

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